A History of the Treatment of Renal Failure by Dialysis

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To Fernando Valderrábano, because without intending it, he was responsible for my writing this book. His untimely death as it went to press has saddened us all.

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Preface

This is not the first history of dialysis, nor will it be the last. However, the present seems a useful time to draw together the series of extraordinary events which led to the invention, introduction and application of this form of medical technology, the first functional substitution for a failing human organ. The events are now long enough ago to achieve a reasonable perspective; and yet we are privileged still to be able to hear directly from a number of the pioneers of the earliest days of dialysis from more than half a century ago such as Kolff and van Noordwijk, Bywaters and Joekes, Skeggs, Thorn, Legrain, and also many others who participated a little more recently in the 1950s and beyond. I have also had the privilege to know and discuss dialysis with many of those key figures who are no longer with us—Nils Alwall, Jean Hamburger and John Merrill amongst them.

It is an extraordinary story indeed: for me, the crossroads was in 1937 in the city of New York, when William Thalhimer used the newly purified and standardized heparin from Toronto for *in vivo* dialysis, in an apparatus containing the cellophane sausage skin tubing which had become popular for laboratory dialysis. Hirudin and collodion had made dialysis possible, heparin and cellophane made it practical, and then later on PTFE and silicone rubber made long-term treatment possible. Thus a perceived need for better sausages and more effective insulation for electric wiring played a key role in the history of dialysis, as well as the dogged determination of a few pioneers who persisted against not only their initially poor results, but also against persistent professional opposition or indifference, which it is easy to forget today. As always in advances in medical science, accident and fortune played a role, and as so often war played a role in advancing knowledge and experience—even though, of course, it hindered initial steps towards practical dialysis in the Netherlands.

This book is written with both historians of medicine and those involved in nephrology in mind: I hope that the latter group will forgive some of the simple language and (to them) redundant explanations of terms which are intended to make the message more widely intelligible. I have concentrated also on what has been little—or never—recorded so far; thus I have emphasized Rowntree and Turner's contributions over Abel's leading role, and clearly whilst no-one could ever wish to neglect the outstanding contributions of Kolff and Scribner, they have been discussed elsewhere many times in many other texts, and thus here I have highlighted the work of Murray and Alwall, which is so much less well known. Finally, much of what has been written in the past on the history of dialysis concentrates mostly or entirely on events in the United States, perhaps because many of the most significant changes occurred in that country: I have tried to make this a balanced history, taking note particularly of the many major contributions published in languages other than English.

This book is in two phases: development and consolidation. The first 15 chapters tell the story of the development of machinery and ideas. By 1970 the context of

dialysis had almost completely been established—it was the details of methodology, the complications foreseen and unforeseen, and above all the numbers and type of patients that would change in subsequent decades. This phase is described in the subsequent seven chapters. Perhaps the next phase will be the redundancy of dialysis for long-term treatment of uraemia: only time will tell.

Stewart Cameron
Melmerby, Cumbria
1999–2001

Acknowledgements

A number of specific sources are given in the notes and references who must be thanked for their vital contribution, but I must acknowledge here also at least some of many people who have helped in the preparation of this brief history.

First and most important my associate Jackie Hicks, without whom it could not have been written. Almost no obscure source defeated her. Gabriel Richet put me right on many matters relating to uraemia and the introduction of dialysis to France. David Hamilton gave me access to letters written to him by pioneers of dialysis in the early 1980s, and many of these were invaluable, as well as the numerous other insights he contributed. Håkan Westling gave me information on Alwall, and Shelley McKellar on Gordon Murray from her (then) unpublished thesis. Dr V. Heinze helped ferret out the story of the Halstrup kidney in Germany. Paola Fernandes helped with the early years of dialysis in Brazil. Steve Peitzman gave me access to unpublished material from the United States, and his rich published record on the history of dialysis. Kiyoshi Kurokawa, Akira Saito and Yukihiko Nosé helped with the early history of dialysis in Japan, Fernando Valderrábano for Spain, Hans Gurland and Heintz-Gunther Sieberth for Germany and Tita Fogazzi for Italy. Charles George gave ideas and advice, and a copy of his thesis containing unpublished data from Abel's laboratory notebooks and correspondence concerning his vividiffusion apparatus. Chris Blagg supplied unpublished material on events in Seattle in the early 1960s. Nic Hoenich gave pictures and data from his collection of material on dialysers from 1959, and aided me on many technical matters to do with dialysis machinery. Jacob van Noordwijk allowed me access to the English version of his monograph before publication. Matt Blessing of the Marquette University Library supplied valuable information on Dick Stewart; Patricia Painter of the Henry Ford Hospital on Lam and Murray; and Felicity Pope of the Cardiovascular Museum, Toronto, again on Murray. Sherman Kupfer and Barbara Niss of Mt Sinai Hospital, NY gave me data on Stephen Rosenak. Professor Pat Grollman gave me information about his father's work.

At various times in the past, and more recently, I have been in contact with many pioneers of dialysis in the 1940s, 1950s and 1960s, and have gained valuable personal insights from them that greatly augment the published record: they include Eric Bywaters, Pim Kolff, Nils Alwall, George Thorn, John Merrill, Leonard Skeggs, Marcel Legrain, Walter Roschlau, Jean Hamburger, Mark (Jo) Joekes, Paul Doolan, Paul Teschan, George Schreiner, Bruno Watschinger, Jean Crosnier, Hugh de Wardener, Gabriel Richet, Emilio Rotellar, Frank Parsons, Vittorio Bonomini, Yukihiko Nosé, Luigi Migone, Belding Scribner, Mollie McGeown, David Kerr, William Drukker, Lee Henderson, James Cimino, Stanley Shaldon, Eli Friedman, Dick Stewart and Jack Moncrief.

Finally I would like to thank my fine colleague and good friend Lee Henderson, and Baxter Healthcare, for material assistance in achieving publication of this book.

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Contents

Chapter 1

Why a history of dialysis?

Kidney failure is by no means as common as cancers or heart disease, but by the end of the last millennium nearly one million individuals worldwide, who had suffered complete and irreversible failure of kidney function, were being maintained alive by a 'temporary' treatment: dialysis. The interest of chronicling the development of this treatment arises, not only from its important role in treating patients with kidney disease, but because of the lessons it can teach us about the development of medicine and the introduction of new treatments. The kidney was the first organ for which complete mechanical substitution became possible. This meant that when the idea of treating kidney failure by a machine was first suggested more than half a century ago, neither the medical professions nor those in charge of the delivery of health care were able to comprehend the change that it represented, and most opposed its introduction.

When, another 15 years later, it became possible to treat by repeated dialysis support not only those whose kidneys had failed for a few days or weeks, but to treat also those who had lost kidney function forever, the impact was devastating. The new treatment could, to begin with, be made available only for a few: all the others must die. A whole new set of ethical questions arose, without any means of dealing with the agonizing new questions. The new treatment was expensive in staff and materials, and placed burdens on budgets that could not be met: how many people could the system 'afford' to treat? How could a choice be made?

Finally, the treatment was a not definitive solution: the kidneys were not restored to function, but substituted for. Every few days, people had to renew their chance of existence by treatment on a machine, which replaced only in part the function of their own, failed kidneys. Thus it was archetypical of a 'halfway' technology [1]. As patients lived for years and then decades by dialysis, the terrible consequences of being 'frozen' in a state of kidney failure far longer than could have happened in nature became apparent, with familiar as well as new, unfamiliar problems arising, crippling many long-term dialysis patients. Even worse, some completely new problems arose through contamination of the water and chemicals used for dialysis, and the nature of the machinery, not all of which have been solved yet. Finally, the major form of dialysis, involving a blood circuit (haemodialysis) is carried out for the majority by gathering a number of people together for treatment in dialysis units. These individuals were by their state of suspended kidney failure vulnerable to infection, and the repeated withdrawal and return of blood from each was an invitation for blood-borne infections such as hepatitis to spread. Within 10 years of its introduction for long-

term kidney failure, the world of dialysis was rocked by epidemics of virus-induced liver disease, in which, in a bizarre twist of fate, affected staff died more frequently than patients. Thus the story of dialysis has an importance and interest well beyond the details of its development and introduction, and this is the story dealt with below.

Chronic kidney (renal) failure has never been a condition which has captured the imagination of either the public or of historians, as conditions such as the great epidemic infections did, or even a few chronic diseases such as gout. Thus, despite its importance—both in the emergence and daily practice of the treatment of kidney patients and the science of kidney function and disease that is nephrology—the role and evolution of dialysis has not received much attention from historians of medicine or of nephrology.

Only a handful of short general histories of haemodialysis have been published [2–9]. All are rich in useful and interesting detail, and our debt to William Drukker [4] and Pat McBride [3] is considerable, since they pioneered the field and whose works form the indispensable base for any further enquiry. However, only the works of Cheng [6] and Richet [7] have attempted to place the evolution of the technique in any general historical or intellectual context; but that of Richet is tantalizingly short and without references, and that of Cheng concentrates heavily on events in the United States. Finally, Fagette [9] emphasizes the evolution of scientific knowledge of the detailed biophysics of membranes, diffusion and ultrafiltration[1].

In parallel with developments in extracorporeal haemodialysis, dialysis of the supposed toxins accumulating in kidney failure directly from the blood vessels lining almost every body cavity was investigated as a treatment for uraemia using irrigation of fluid into and out of the cavity. However, only dialysis employing the peritoneum has played any enduring role in the treatment of renal failure, although the story of how other cavities were explored is of interest in a historical context. The history of *peritoneal dialysis* has been described briefly by McBride [8], Palmer [10] and Gokal and Nolph [11], and in several other even briefer reviews [12], but the most detailed treatment to date again has been that of Wiliam Drukker [13].

The history of dialysis is no different from the history of any other medical or scientific topic. With the benefit of hindsight, it is all too easy to edit the story into a smooth progression, advance following upon advance in a logical and seemingly inevitable fashion. In truth, as will be evident throughout this book, the reality is almost always a much more messy process, with ideas forgotten or neglected, and later rediscovered more than once, false starts, blind alleys and periods of stagnation. Questions, ideas, techniques and treatments which are now forgotten were once the source of great interest and controversy, and these byways contributed to the study and development of the ideas and treatments which have endured. It becomes obvious also how much empiricism and trial and error led to improvements in dialysis techniques, as much as scientific advance or new materials. Again, we must not make too logical the advance of the art in this area or any

[1] Only when this manuscript was almost completed did I have the opportunity to see the monograph of Jacob van Noordwijk (*Dialysing for life. The development of the artificial kidney*). Kluwer, Dordrecht, in press). Several references to this work have been added to the text below.

other: whilst technology had much to contribute to the evolution of haemodialysis, empiricism had an even greater role to play.

We need to consider also the characteristics of the society which shaped the history: how were acute potentially reversible, or chronic irreversible, renal failure regarded by people in the nineteenth and the first half of the twentieth century? In truth, they were regarded very little, even though many sources of data suggest that chronic renal failure in the teeming cities of early industrial England was as much as 10 times more common than it is today. This remained the case until the early years of the last century, up to the First World War [14], just as it remains in the developing world at the end of the twentieth century [15]. The few notable figures dying of uraemia such as Samuel Johnson, Mozart (possibly), Beethoven, Disraeli, Brunel and (more recently) Jean Harlow did not impinge their renal failure on the public of the time, or since. There was no public consciousness of renal failure, as there was of, for example, syphilis, tuberculosis [16] or even gout [17]. Patients died slowly—and generally quietly—of uraemia at home or in hospital without causing any fuss. The only visible sign of renal failure was the swelling of dropsy, with which renal disease had been long identified [14,18], but this was confused with the majority of cases of dropsy arising from heart failure and from liver disease, and was regarded as a disease *per se*.

Thus it is impossible to know from what condition the 'hydropic' woman in Gerard Dou's famous painting in the Louvre (Fig. 1.1) may be suffering from [19]. This was changed only when Richard Bright established the connection between dropsy with

Fig. 1.1 Detail from *The Dropsical Woman (La Femme Hydropique)* by Gerard (Gerrit) Dou (Musée du Louvre, Paris). The focus of the painting is twofold: the sick oedematous lady being fed from a spoon whilst her child watches anxiously, and the doctor earnestly examining her urine in the traditional round-bottomed matula. The art of uroscopy in diagnosis dated back to Byazantine times and before [19], but dropsy was only connected with kidney disease in the early nineteenth century.

albumin in the urine and renal alterations in the 1820s and 1830s, which changed the name of the condition for the next century to Bright's disease, and introduced the idea of eponymy to medicine.

I have not succeeded in tracing any novel in English, or other work of art, from this time to the middle twentieth century that even mentions chronic kidney failure [20]. Perhaps this was because the kidneys normally function quietly and unobtrusively, and only if obstructed might signal their presence by pain and anuria. They were not associated in the public mind as being obviously necessary for the continuation of life, as the lungs or heart were. Acute renal failure remained even more hidden, since (as we shall see) it did not impinge even on medical consciousness until the two great world conflicts of the twentieth century.

Acute and chronic renal failure were then reframed rather abruptly around 1950–1960 by the introduction of dialysis [18] and then transplantation: from this point on, they were seen in relation to the machines used for treatment and the placement of new, healthy kidneys into sick recipients. During the 1950s, newspapers and magazines attest much public interest in the new kidney machines [18], and the controversy they aroused: could the complex functions of a human organ be replaced even temporarily by a machine? Was the prognosis of those with temporary renal shut-down *really* made better by treatment with the artificial kidney? A decade later, chronic renal failure entered the public stage mainly as a package of problems involving dreadful choices of who should receive long-term life-saving treatment on the 'artificial kidney', with machines always in short supply; the ethical and social debates generated by transplantation in general; and, finally, the problem of resource allocation as the high cost of both these treatments became evident.

In this general history, I will try to show how the interplay of scientific concepts and the dogged persistence of a few strong individuals against initial failures led to the introduction of dialysis. I wish to emphasize particularly, however, the crucial role played by the *availability of new biological or synthetic materials in permitting the science of dialysis to be applied to the clinical problems of kidney failure*: dialysis membranes, anticoagulants and plastic polymers. Without these new materials, the pioneers of dialysis from the 1940s to the 1960s would have been as impotent as their predecessors were when faced with renal failure. I will discuss also, but rather briefly, how social, medical, political and financial events influenced the introduction and expansion of the technique. Where there are excellent accounts already available—for example the work of Kolff during the Second World War in the Netherlands (see: van Noordwijk and Chapter 8), or literature on the introduction of long-term dialysis in Seattle in the early 1960s (see: Chapter 14)—I have been relatively brief, to allow more detailed exploration of those byways or lost facts and ideas which have received less attention in the narrative we already have.

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3. McBride PT. *Genesis of the Artificial Kidney*. Baxter Healthcare, Chicago, 1987. McBride also assembled an extensive range of early dialysers, most illustrated in his book, which remain in the possession of the Baxter Corporation, Round Lake, Illinois, USA and form the most comprehensive collection of material relating to artificial kidneys extant. There are also major collections of early artificial kidneys in the International Center for Artificial Organs and Transplantation (ICAOT) in Cleveland, currently on loan to the International Center for Medical Technologies collection: 6410 Fannin, Suite 450, Houston, TX 77030, USA (Julia Glueck); the Smithsonian Institution National Museum of American History, 14th Street and Constitution Avenue NW, Washington DC, USA (Judy Chelnick). The Deutsches Medizinisches Museum, Anatomiestrasse 18–20, D-84049 Ingolstadt, Germany (Dr Christa Habrich) and the Boerhaave Museum, Agnietenstraat 10, 2312 WC Leiden, the Netherlands (Dr GAC Veeneman) have artefacts mainly relating to Kolff. There are occasional other single machines in other museums, such as the early Kolff dialyser in the Science Museum, South Kensington, London, UK; and material from individuals such as that relating to Gordon Murray can be found in the Cardiovascular Museum, Toronto General Hospital, Canada, and to Nils Alwall in the Museum of Medical History, Lund. Finally, apart from the holdings on Kolff in the Smithsonian Institution, the Marriott Library of the University of Utah, 295 S 1500 E, Salt Lake City, UT 84112–0860, USA has a major collection of papers, photographs and artefacts relating to him in the special collections division of the university library (Dr Stan Larson). A list and details of collections relating to artificial organs in general can be found on the website of the 'Project Bionics: preserving, researching and promoting the history of artificial organs' of the Smithsonian Museum, Washington DC (Dr Shelley MacKellar): *www.nlm.nih.gov/hmd/manuscripts/asaio/index.html*

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13. Drukker W. History of peritoneal dialysis. In: Maher JF, ed. *Replacement of renal function by dialysis*, 3rd edn. Kluwer, Dordrecht, 1987: 475–515. This history does not appear in subsequent editions. It is the most detailed history of peritoneal dialysis yet published.

14. The main source of data supporting this statement is the national register of causes of death in the United Kingdom. Despite changes in terminology, it is clear that the death rate from 'nephritis' in the middle nineteenth century was over 600/million population/annum, and fell steadily from the beginning of the twentieth century to less than one-tenth of this by the mid century, remaining relatively constant thereafter. Bright himself commented on how common what we would now term the nephrotic syndrome was in London of the 1820s and 1830s, with a population of only a million and a quarter inhabitants in the 1831 census: 'I believe that I speak within bounds when I state that not less than 500 die of it [Bright's disease] annually in London alone.' (*Guy's Hosp Rep* 1836; **1**: 316). This represents an incidence of 0.4 %—10 times the incidence in SE England during the 1960s (see data from Cameron [15]).
15 Data on the true incidence are, of course, lacking in the developing world, but comparative figures for percentage of hospital admissions are available. Using this crude index, data from all over the developing world show an incredible 2–4% of all admissions arise from nephrotic renal disease. The comparative figure for North America or the United Kingdom (and China) is 0.04–0.06%. For more details see: Cameron JS. The natural history of glomerulonephritis. In: Kincaid-Smith P, d'Apice AJF, Atkins RC, eds. *Progress in glomerulonephritis*. Wiley, New York, 1979: 1–25. See also: Kibukamusoke J. Historical background. In: *The nephrotic syndrome of quartan malaria*. Kibukamusoke J. Williams & Wilkins, Baltimore, 1973.
16. Dormandy T. *The white death. A history of tuberculosis*. Hambeldon Press, London and Rio Grande, Ohio 1999. This is only the most recent of a number of histories of this malady, whose impact on the consciousness of Western man has only been equalled by the great plagues and, perhaps, venereally
transmitted diseases.
17. Porter G, Rousseau GS. *Gout: the patrician malady*. Yale University Press, New Haven, 1998.
18 Peitzman SJ. From dropsy to Bright's disease to end-stage renal disease. In: Rosenberg C, Golden J (eds) *Framing disease: the creation and negotiation of explanatory schemes. Milbank Q* 1989; **67** (Suppl 1): 16–32. For examples of popular accounts of early dialysis machines, see Chapter 5, ref. [10] and Chapter 8, refs [26,27] below. In every country, when haemodialysis was introduced numerous articles appeared in the popular press and magazines dealing with the new technology.
19. The iconography of dropsy is very limited compared to the many genre paintings and drawings—and even some religious works—showing, as in Dou's painting, the physician earnestly examining a round-bottomed matula full of urine. This process had nothing to do with the physical diagnosis of kidney disease, however, but was an act of divination rather than diagnosis. See: Fine L. Circle of urine glasses: art of uroscopy. *Am J Nephrol* 1986; **6**: 307–11; Haber MH. Pisse prophecy: a brief history of urinalysis. *Clin Lab Med* 1988; **8**: 415–30; Dal Canton A, Castellano M. Theory of urine formation and uroscopic diagnosis in the medical school of Salerno. *Kidney Int* 1988; **34**: 273–7; Fogazzi GB, Cameron JS. Urinary microscopy from the seventeenth century to the present day. *Kidney Int* 1996; **50**: 1958–68.
20. I have also been unable to find any descriptions in German, Spanish and Italian literature. However in French, in the massive chronicle *Les Thibaults* by Roger Martin du Gard (1881–1958), winner of the Nobel Prize for literature in 1937, there is a detailed description of a decline and death in uraemia: *La mort du père. Oevres complètes, Tome 1*. Bibliothèque Pléiade, Paris: 1250–301. However this description is framed in a very dramatic way with

severe pain, repeated convulsions, remissions and relapses, anuria and diuresis, from some unstated (but presumably obstructive) cause whose investigation and possible treatments are never discussed; altogether not a very faithful account of a typical death in uraemia. I am grateful to Professor Alain Meyrier for drawing my attention to this description. Since the introduction of dialysis, this treatment has formed the theme of several works, for example the novel *The Stockholm syndrome* by Jonathon Havard, published in 1986.

As we go to press, we learn that tragically, the unique collection of early dialysers and other related apparatus collected by Pat McBride has been destroyed in error.

Chapter 2

Replacement of body function by mechanical means

Replacement of body parts is not a new idea, and the 'artificial kidney' or haemodialyser can be seen today as part of a spectrum of objects, which only recently have developed into biomechanical devices (Fig. 2.1). In parallel with ideas of transplantation of fresh body parts from other human beings or animals to replace diseased ones [1] has run the idea of mechanical substitution. Externally applied examples of prostheses designed to replace lost parts must have started with the earliest crutch to substitute for a lost leg, whose origins are not recorded; but prosthetic noses and toes [2,3] have been found in Egyptian mummies to replace those destroyed by disease, lost in accident or battle, or cut off as punishment. There seems little doubt that at least the toe was worn during life, and was not merely substituted after death so that the mummified corpse would be complete in the after-life [3]. The existence of ancient Egyptian dentures is controversial [2], but they were certainly present in the classical world, and over the centuries and throughout the world were successively made of wood (Fig. 2.1c), ivory, metal, porcelain and—more recently—rubber and plastic polymers [4].

Metal eyes were used to replace those lost, again from Egyptian times onwards, later being made of gold and silver in the hands of Ambroise Paré (1510–1590). Glass eyes were introduced only at the end of the eighteenth century, initially as a cover to the open orbit, but by the end of the nineteenth century, with access to better technology, as a light, blown globe to fill the orbit [5]. Paré was also one of those who advanced the design of artificial limbs (Fig. 2.1b), which had been made from various materials from classical times onwards: wood, cloth and sometimes metal [6], as in the famous iron hand of Slovakia. Finally, in a slightly different category, are spectacles to assist failing vision by correcting externally defects of focus; one might even include the ear trumpet in this group. In the past 40 years, more sophisticated *internal* prostheses have been used, such as replacement joints, starting with the hip in the 1960s but moving on to knee, ankle and finger, and of course internal placement of acrylic lenses within the eye [7], carbon fibre tendons and, finally, artificial valves to replace defective ones within the heart (1952) or woven acrylic tubing to replace diseased blood vessels. A parallel development of such external and internal prostheses for the maimed or diseased has been to provide what nature did not endow, or was thought to have endowed inadequately—from padded cod-pieces or brassieres to silicone mammary implants.

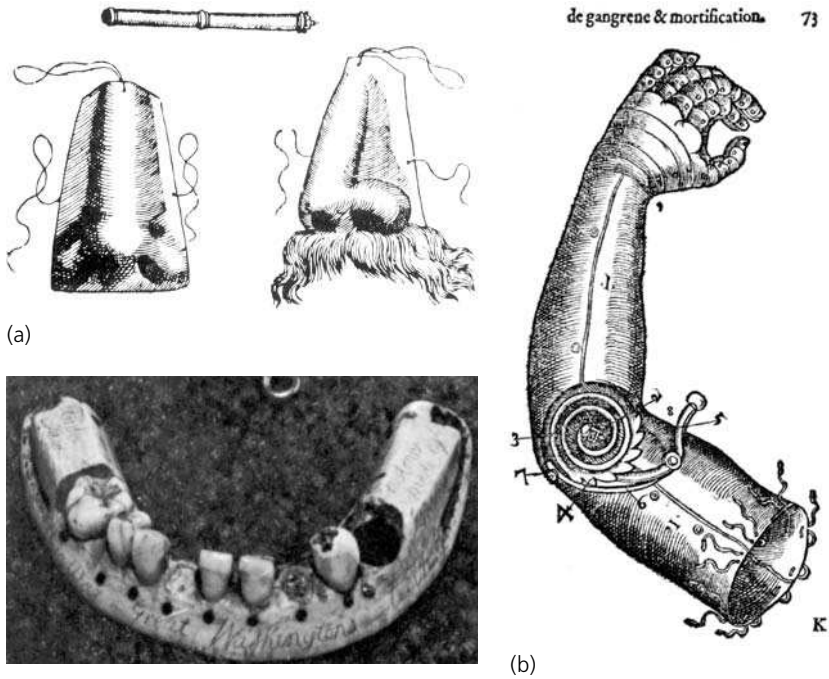

Fig. 2.1 Various replacement parts. The nose and surprisingly sophisticated artificial arm (a, b) are from Ambroise Paré's *Ten books of surgery* Paris, 1582 (Académie de Médicine, Paris), whilst (c) shows George Washington's wood-based dentures, now in the New York Academy of Medicine.

All of these devices, however, merely function by presence: nothing more is required of the prosthesis or implant beyond its integral survival. However, once the idea of the body as a machine governed by physical laws had been established through the work and ideas of Harvey, Borelli, Hales and many others in the seventeenth and early eighteenth centuries, a natural implication was that mechanical substitution of *function* should be possible. Perhaps a more diligent search than my own will reveal mention of this idea during the nineteenth century. This idea, however, generally lay dormant until well into the twentieth century, probably because the sheer complexity of the functioning of any body organ deterred anyone from actually attempting total organ replacement.

Haemodialysis is today only one example of the function of a body part being taken over by a machine, but is notable in being the *first* in which the function of the organ was replaced, rather than assisted. The only precedent in its application to man is *assisted ventilation* (Fig. 2.2). Into the first half of the twentieth century, paralytic poliomyelitis remained a scourge in all developed countries. Many recovered with withered limbs to testify to their encounter with the virus, but many others died, often from paralysis of the respiratory muscles so that they suffocated, unable to breathe. In

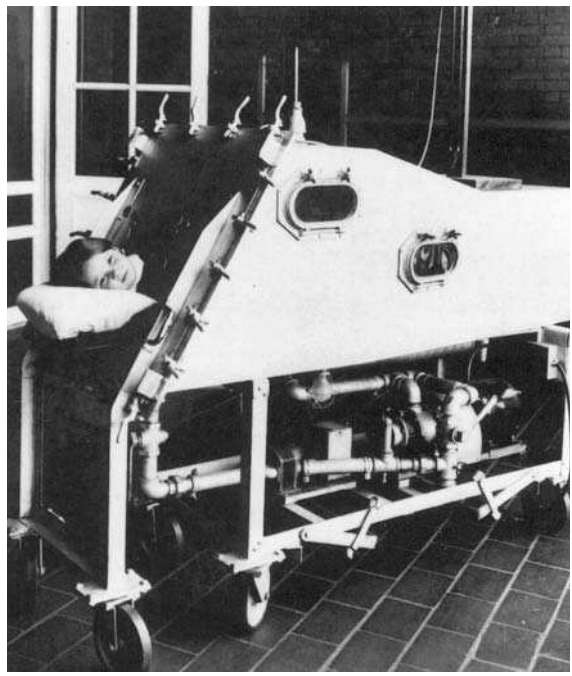

Fig. 2.2 A child in an 'iron lung' designed and built by Charles Drinker. (Courtesy Alan Mason Chesney Archives, Johns Hopkins Hospital.)

1929, the public health engineer Paul Drinker (1894–1972) and Dr Charles McKhann treated a victim of poliomyelitis who was unable to breathe, using a machine which assisted breathing by applying intermittent external negative pressure [8]: the memorably named 'iron lung' was born (Fig. 2.2). This type of machine continued in widespread use until the 1950s, when both the control of poliomyelitis in the developed world by immunization, and the introduction of positive pressure ventilation down a tube into the trachea during the Copenhagen polio epidemic of 1952—one of the last major outbreaks in Europe—signalled its end. However, during treatment by external negative pressure ventilation, the lungs continued their own work in terms of gas exchange—only their movement in ventilation was taken care of [9].

Neverthless, a Rubicon *had* been crossed: these patients on iron lungs—unlike the hosts of a glass eye or an artificial limb (replacement hip joints and heart valves were well in the future in the 1930s)—were dependent for their survival on the continuing function of a machine. It is salutary to remember how close we came in the 1940s and 1950s, with long-term ventilation of those paralysed by poliomyeltitis and dependent on a ventilator, to a similar situation as that experienced with long-term dialysis in the 1960s. This 'solution' to the problem of paralytic polio with inability to breathe was in every way comparable to dialysis, a 'halfway technology' [10] that did not cure or reverse the condition but could tide the patient over a period of failure, but perpetuated it in those who never made a spontaneous recovery after a period of

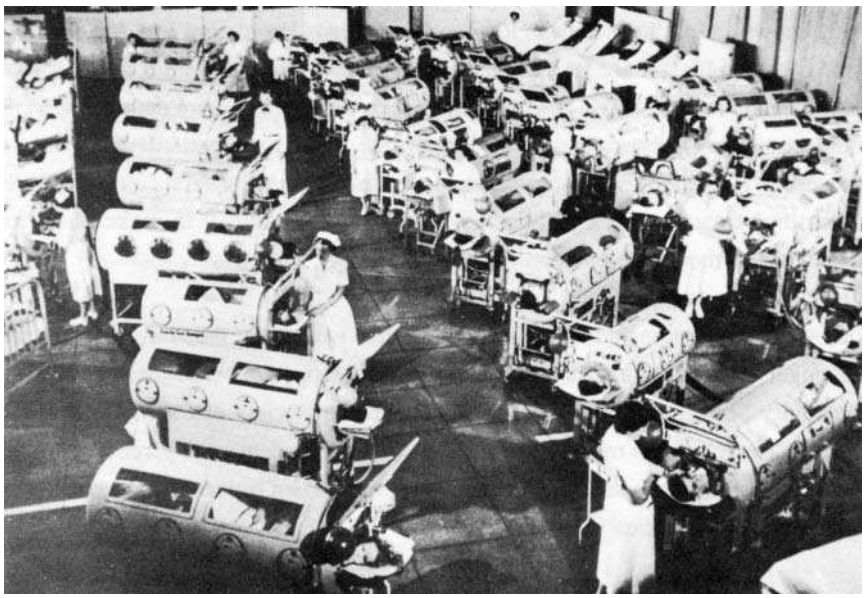

Fig. 2.3 A 40-machine artificial ventilator ('iron lung') unit for the treatment of acute cases of respiratory failure from poliomyelitis in Rancho Los Amigos Hospital, Los Angeles, in the 1950s. (From [7] with permission.)

support. The advent of lighter, smaller, easier-to-use positive pressure machines during the 1950s must inevitably have led to demand for widespread use of long-term ventilation, with ventilator units everywhere—had it not been for a definitive advance which warded off this difficult situation, at least in the developed world. The picture of what appears to be a 40-machine unit in Los Angeles at Rancho los Amigos in the 1950s is eerily similar to a photograph of a dialysis unit in the 1960s or later (Fig. 2.3).

This definitive treatment which came 'over the hill' only just in time was, of course, successful immunization against poliomyelitis, first using the killed virus vaccine which Jonas Salk (1914–1995) and his colleagues produced in 1953, followed rapidly by the live attenuated vaccine of Albert Sabin (1906–1993), introduced in 1955. In the developed world, epidemic and endemic poliomyelitis disappeared within only a few years, and 'iron lungs' were rapidly consigned to museums of medical equipment. However, the lesson of their use for more than 20 years remains: prevention is the real cure, not palliation by expensive and inconvenient technology (see Chapter 22 for further discussion of this topic).

The idea of replacing renal function by a machine was first articulated in August 1913, not in a scientific paper but—as we shall see later in Chapter 5—in anonymous reports from newspapers, the London *Times* and the *Chicago Journal*. When in June 1955 the American Society for Artificial Internal Organs (ASAIO) was founded [11], there was in fact just one whole organ for which an artificial replacement was then available—the kidney—and that for a limited period only. Under these circumstances the name of the Society could be considered hubris, but since has been amply justified.

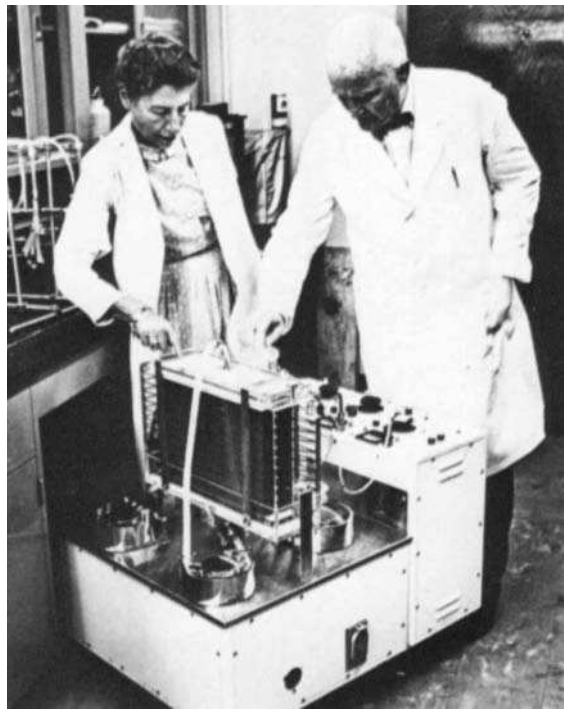

Fig. 2.4 Dr John Gibbon and his wife with their heart–lung machine, used in May 1953 to correct a septal defect under total extracorporeal bypass. The development of extracorporeal circuits for cardiac surgery was in parallel with that of the development of the artificial kidney, and was advanced also by the introduction of new materials during the 1950s (see text and [10]).

It is true that, as we shall see later, the idea of an extracorporeal circuit began in the early nineteenth century, and attempts to replace the heart's action by pumping blood mechanically were well developed by the end of that period. However, the idea of a complete artificial heart, rather than just valve replacement was suggested only in the mid-1950s, for example at the 1957 meeting of the ASAIO by Peter Salisbury in his presidential address. Complete extracorporeal cardiopulmonary bypass in animals was achieved first in 1939 by John H. Gibbon (1903–1973) in the United States after 7 years' work, but it was not until May 1953 that the first cardiac operation under cardiopulmonary bypass was performed by him in a patient: closure of septal defect (Fig. 2.4). A left ventricular assist device was placed in man in 1963, and an early mechanical heart in 1969, both by Denton Cooley (b. 1920) at Baylor College of Medicine, Houston, Texas. However, nothing more was done in this area for more than a decade whilst mechanical problems were studied, and the artificial heart is really a story of the 1980s onwards. It is of interest also that Willem Kolff, one of the major pioneers of the artificial kidney in the 1940s and 1950s, devoted his life from the mid-1950s onwards to the struggle to achieve a successful, implantable mechanical heart.

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9. The iron lung is often referred to—even by its inventors—as a 'respirator': it is a *ventilator.* The idea of *extracorporeal gas exchange* using bubble and disc oxygenators arose from adaptation of work in the nineteenth and early twentieth centuries on extracorporeal whole organ perfusion in animals, by John Gibbon in the USA (Fig. 2.4) during the 1930s;

it was only applied to man in 1951 by Dogliotti and Costantini of Torino, Italy—who, as we shall see in Chapter 11, also built and used an early artificial kidney 2 years later. Gibbon then applied an oxygenator to complete cardiopulmonary bypass in humans in 1953 (see ref. [9]).

10. Hewitt RL, Creech O Jr. History of the pump oxygenator. *Arch Surg* 1966; **93**: 680–96. Membrane oxygenators arose directly from work on artificial kidneys, since dark venous blood obviously became red during passage through the apparatus. Apart from Murray's work in the 1940s, discussed later, as early as 1951 Karlsson and colleagues in Sweden described an oxygenator which used cellulose membranes. The Kiil kidney was intended, and actually used as a membrane oxygenator (see Chapter 12, ref. [30]).
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Chapter 3

The science of dialysis: 'uraemic toxins'

Before the concept of treating renal failure by dialysis could arise, two ideas had to be present first: (i) that in some way loss of renal function leads to the accumulation, in the blood and other body fluid, of substances normally excreted, which contribute to or cause the illness and subsequent death of the individual; and (ii) that these substances might be removed from the blood (and secondarily from the tissues) by processes of diffusion or dialysis.

The early evolution of the idea that sees the state following failure of kidney function—'uraemia'—as a chemical and regulatory imbalance has been outlined by Richet [1–3]. Our understanding of this complex state remains incomplete even today [4]. The earliest relevant observations were that urine was the product of the kidneys—an observation that must have been made at a very early date and it has been said since antiquity that 'every butcher knows that the kidneys make urine'.

However the 'father of medicine', Hippocrates (b. 460 BC) did not himself comment on the origin of urine, whilst Aristotle (384–322 BC) placed its origin in the bladder. The task of solving the problem was left to their successor Cornelius Galen (129–216+ AD), who described the origin of urine in some detail [5]:

> thus it is that urine is secreted from the blood by the kidneys and passes hence through the ureters to the bladder, from which it is discharged at a suitable time when reason gives the command.

Much later, it was noted that suppression of urine, leading to its retention in the blood, converted this into a fluid similar to urine [6]. This phenomenon was most obvious when the cause of the renal failure was obstruction of the urinary tract, which was much more common in an era when urinary tract stones were themselves much more common than they are today in developed countries. Several descriptions of the urinary smell of patients with renal disease, and of their dejecta and fluids *post mortem*, were made during the sixteenth to eighteenth centuries, including an account by the great Dutch teacher Hermann Boerhaave (1668–1738) [6]. He noted, in a lawyer with urinary obstruction whose history is given in detail, that 'a liquid resembling urine was found in the ventricles of the brain' at *post mortem* examination of the body. From such observations Andreas Vesalius (1514–1564) and Albrecht von Haller (1708–1777) were stimulated to remove both kidneys, or tie the ureters, to examine the role of the kidneys in the animal economy [7]. In Haller's case he noted a

'*vomitus urinosus*' in the animals before they died. Thus the idea that the kidneys were responsible for removing noxious substances from the body through urine was already well developed by the eighteenth century.

During the eighteenth century, also, the modern chemistry of body fluids began, and as part of the analysis of urine large quantities of a 'soapy' substance were noted, again by Boerhaave [8] and later by the Parisian chemist Rouelle le Cadet (1718–1779) in 1773 [9], who compared the urine of several species including man. This 'soapy' substance was studied in much more detail in Paris by the physician Antoine Fourcroy (1755–1809) and the pharmacist Nicolas Vauquelin (1763–1829) between 1797 and 1808 [10–12] as part of their gigantic investigation of urinary constituents and renal stones [3]. They crystallized and analysed this substance, showed it contained large amounts of azote (nitrogen) and named it 'urée'. With amazing prescience (given that at that time urea had not even been shown to be present in blood), they suggested [12]:

> it is from the blood arriving by the renal arteries that this azotic matter is separated, and it is thus that this vital liquid, in losing the superabundance of this substance, achieves and conserves the constancy of composition which is necessary to it.

They thus also anticipated Claude Bernard's 'milieu intérieur' by 50 years. Even more amazingly, at this very early stage they speculated on the possible toxicity of urea:

> it is extremely probable that when urea is not separated from the blood, the overload of these elements, and above all urea, is capable of causing diseases.

However, when later in 1821, together with Ségalas [13], Vauquelin proceded to test this idea by injecting urea intravenously into animals he observed no toxicity, only a diuresis. This was the first of many similar studies during the following century and a half that continued to give conflicting results, most confirming that urea was not toxic but many others claiming various effects. In the same year of 1821, however, in Geneva, Jean Louis Prévost (1790–1850) and Jean Baptiste Dumas (1800–1884) showed in the blood of animals submitted to extirpation of both kidneys, that urea concentrations rose in a progressive fashion until death occurred [7,14]. What about in man? Only 6 years later in London, both the associate of the immortal Richard Bright's at Guy's Hospital, London, John Bostock (1773–1846) and another renowned physician-chemist, William Prout (1785–1850) [15] showed independently that urea was present in the blood of patients with renal disease as its excretion in the urine diminished, and later that it was present also in smaller quantities in the blood of normal individuals. This work was confirmed and much expanded in 1829 by Robert Christison (1797–1882) [16] and J.C. Gregory [17], both working in Edinburgh, and also at Guy's by another of Bright's pupils and associates, the chemist and clinician George Owen Rees (1813–1889) [18]. At that time the analysis of urea was imprecise and required large amounts of blood, and so was rarely performed, even as a part of chemical studies of clinical renal disease. Rees made the important observations that at *post mortem* urea was present throughout all body fluids, including cerebrospinal fluid, ascites and pleural effusions.

Christison (later Sir Robert) (Fig. 3.1) can be credited as having, for the first time, put forward the idea of a toxic state in renal insufficiency from a combination of

(a)

ON

GRANULAR DEGENERATION

OF

THE KIDNIES,

AND ITS CONNEXION WITH

DROPSY, INFLAMMATIONS, AND
OTHER DISEASES.

BY

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CLINICAL MEDICINE, IN THE UNIVERSITY OF EDINBURGH, &c.

EDINBURGH:
ADAM AND CHARLES BLACK, NORTH BRIDGE:
AND LONGMAN, ORME, BROWN, GREEN, AND LONGMANS,
LONDON.
MDCCCXXXIX.

(b)

Fig. 3.1 (Sir) Robert Christison (1797–1882) of Edinburgh, Scotland (a), who first articulated in 1839 a theory of uraemia based on the retention of solutes, particularly urea, in his book of 1839 (b). (Courtesy Royal College of Physicians of Edinburgh.)

factors, including the retention of chemical substances, in his important but still neglected book of 1839 [16]:

> ultimately its [i.e. granular kidney] intrinsic result is to overwhelm the functions of the brain, probably in consequence of the blood … being, on the one hand, poisoned by the accumulation of urea, and deprived on the other of its colouring matter.

He carefully noted, however, that there was no correlation between the concentrations of urea in the blood and the clinical severity of the disease. In this book—as this quotation suggests—he also described, defined and quantified the anaemia of chronic renal failure by studying the proportion of 'haematosine', as haemoglobin was called at that time [16,19]. Anaemia was to prove the major debilitating factor for patients maintained on dialysis 125 years later. Both these observations on urea and anaemia were re-emphasized soon after by the great French physician Pierre Rayer (1793–1867) in his major encyclopaedia and atlas of renal diseases, published only a year later [20]. Rayer added the use of the microscope to the investigation of his patients' urine, and although he noted a diminution in the number of red cells in the blood, there were no techniques for a further decade to allow quantification of this [19].

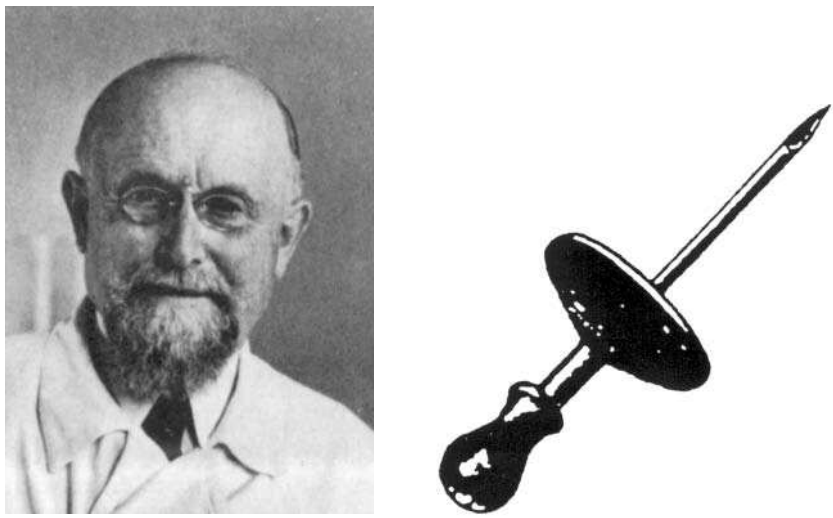
The concept of uraemia as 'urine in the blood' was advanced by Pierre Piorry (1794–1879), who described 'contamination du sang par l'urine' in 1840, but who in 1847 designated the state 'urémie' [21] not 'urinémie'. The true complexity of the uraemic state is still not resolved more than 150 years later [4], and this early overemphasis on the accessible and quantitatively dominant substance urea remains with

us today in its use as a surrogate to calculate the efficiency of dialysis, by such indices as the Kt/V_{urea} (see Chapter 17). Improved methodology for the measurement of urea, introduced by Justus von Liebig (1803–1873), allowed Joseph Picard (1834–1896) of Strasbourg to describe in 1856 the actual extraction of urea from the blood by the kidney; he noted that the renal vein contained only 60% of the concentration in the renal artery, a difference abolished by tying the ureter [22] and thus stopping renal function. The idea of 'urämische intoxication' was advanced also by Theodor Frerichs of Berlin (1819–1885), who again demonstrated that urea itself seemed not to be toxic, even when injected into animals from which both kidneys had been removed [23]. But if urea itself was not the culprit, what was? Frerichs suggested as an alternative that ammonium carbonate might be the agent mainly responsible, and this view was popular for some years. Thus, by the mid-nineteenth century the idea of the uraemic syndrome as a functional state, principally affecting the nervous system [16,24] and dependent upon the retention in the blood of toxic substances normally excreted in the urine, was already a mature concept.

Sadly, however, most of these chemical insights were lost to view during the following half century, in which the rapidly developing anatomic, histologic and then bacteriological views of disease seemed to provide a better vehicle for understanding. It was only at the turn of the twentieth century that clinical chemical pathology returned to centre stage and major advances followed, again principally in Paris but also in Berlin and London. One can propose several reasons for this prolonged neglect: the first was that clinical chemistry, for the practising doctor and his (there were almost no women doctors at that time) patients, had simply failed to deliver. For all the understanding of the composition of stones and urine chemistry gleaned by Vauquelin, Fourcroy, Marcet, Bostock, Prout and their colleagues, there was not one patient who had thereby been spared the colic, or the knife. In 1848, the wise Dublin physician Robert Graves (1797–1853) who was known also for his strong opinions, wrote [25]:

> As to any benefits served from analytical chemistry in solving the problems of vital action or elucidating the functions of the various organs in health and disease, they may be said to be few, unimportant and inconclusive.

Another factor was the simple one that chemical tests of the day required quite large volumes of blood, such as 50 ml for the estimation of urea (although a new easier hypobromite method for the measurement of blood urea was available from 1880), and blood was not readily available to clinical chemists for study during the latter half of the nineteenth century. By 1850, the practice of therapeutic blood-letting, variably employed since classical times, was falling into history even in blood-thirsty France [26], following the publication of the *Recherches sur les effets de la saignée* in 1835 by Pierre Louis (1781–1872) [27]. For the next half century, if blood was wanted for study, a cut had to be made into a vein with a lancet, or incisions in the skin 'cupped' to extract blood from the wounds. Finally, it was not until the introduction by Hermann Strauss (1866–1944) in Berlin of a hollow needle for drawing blood (Fig. 3.2) in 1898–1902 that blood became easily available again [28]; from such simple ideas are advances made! Access to the blood stream was also made possible by the idea of hollow needles, without which dialysis would be



(a) (b)

Fig. 3.2 Hermann Strauss of Berlin (a) who introduced the idea of using the hollow needles (b) already in use for subcutaneous injections to aspirate venous blood in 1902. This simple idea made it possible to obtain blood easily for clinical chemical measurements, and later made access to the circulation for dialysis a reality. Strauss, a Jew, died in a Nazi concentration camp in 1944. (From Richet with permission. See permissions. [28].)

impossible today: yet how many of those working in dialysis now have ever heard of Strauss?

However, during this fallow period of 50 years some progress was made in the understanding of uraemia, summarized in detail by Ascoli [29] at the turn of the century, when interest in the chemistry of uraemia re-awakened in Paris. In 1859, Treitz of Prague developed the theory of Frerichs further, introducing the (correct) idea that the dissolution of urea to ammonium occurred principally in the gut from urea secretion and ammonium absorption; but ammonium carbonate proved non-toxic, like urea, when injected. These inconclusive results led others such as Schottin [30] in 1853, and a decade later Jaccoud, to propose that creatinine from muscle breakdown caused the uraemic syndrome. In 1865 Sir William Roberts of Manchester (1830–1899) [31] suggested that nitrogenous substances 'intermediate between urea and albumin' were the cause of uraemic symptoms—probably the first articulation of the 'middle molecule' hypothesis (see below). In 1868, von Voit [32], after injecting urea (which he found to be toxic) and other metabolites, suggested that retention of multiple urinary ingredients might be the cause. Maher [33] describes also little-know work done on this subject in the United States in this period.

The role of potassium in determining ultimate death in uraemia was signalled by Victor-Timothée Felz (1835–1893) and Charles Ritter (1837–1884) of Strasbourg, who moved to Nancy after the Franco-Prussian war delivered their former town to

Germany. They showed in a series of papers in the 1870s and 1880s that in animals with ligated renal pedicles dying of uraemia [34], 'the true agents of the intoxication are almost always potassium salts which accumulate in the blood'.

Yet again, they showed that urea could not induce the convulsions and death that the animals suffered after 3 days of uraemia, nor could ammonia or its salts be responsible, as Frerichs had suggested, or creatinine or a number of other urinary constituents. Nevertheless, other workers seemed able to show toxic effects, and the argument continued into the era of clinical dialysis as to whether urea was or was not, of itself, toxic. Numerous other substances were then suggested to be the 'cause' of uraemia—the acidosis (von Jaksch, 1887) and various poorly identified toxic substances extracted from urine (Bouchard, 1887). The exact nature and scope of uraemic 'toxicity' remained obscure to the end of the nineteenth century [29] and indeed still eludes us at the beginning of the twenty-first century [4].

Even in the early 1900s, the clinical syndrome of 'uraemia' was still thought of mainly in terms of *neurological complications*, as in the time of Bright and Addison, and was poorly distinguished from the effects of associated severe arterial hypertension, with or without intracranial bleeding, or from water intoxication. It was Franz Volhard (1872–1950) who articulated in 1918 a more modern view, separating the effects of hypertension as 'pseudouraemia' [35] from those which might be the result purely of renal dysfunction. The concept of a hypertensive encephalopathy was only fully developed by Fishberg in 1928 [36], in parallel with the earlier histological descriptions of accelerated, vicious-circle hypertension between blood pressure and kidney damage by Volhard and Fahr in 1918. Meanwhile even more putative uraemic toxins were advanced, reviewed by Harrison and Mason in 1937 [37]: guanidines (Foster, 1915), phenolic compounds (Becher, 1925) and so on. By this time it was clear that uraemia was a highly complex state, which clearly could be related to lack of renal function, but not to any satisfying hypothesis of causation, or to the retention of any single 'toxin'. The idea of homeostasis in relation to renal disease was developed in the 1920s and 1930s [38], and disordered homeostasis came to form part of most scientists and clinicians' concept of the uraemic state by the time effective dialysis began.

It is interesting to speculate to what extent these ideas of the complex nature of the uraemic syndrome may have influenced the pioneers of dialysis. Judging by what they wrote, it appears that all this work had little if any influence, and that the 'toxic' theory of uraemia remained primary in their minds and motivated them to try and remove diffusable solutes, above all urea. In his classic work of 1947, *New ways of treating uraemia*, Kolff wrote [39]:

> If one asks which substance is to be held responsible for the clinical syndrome of uraemia, this question cannot be answered. By uraemia we mean the state of intoxication which occurs if substances otherwise excreted by the kidneys accumulate in the body. It is not one definite substance that causes the intoxication … it is the sum of all the detrimental influences of the retained substances which leads to uraemia. Up till now not a single substance is known to us which might participate in this intoxication and is NOT removed by dialysis. The clinical improvement of our patients proves that the substances responsible for the syndrome of uraemia are removed by dialysis (p. 77).

Nevertheless in his writings he returns again and again to the removal of quantities of urea, even recording himself on film in 1949 pouring out the urea removed from one patient by dialysis [40].

But before removal or correction of this complex of toxic substances could begin, ideas of diffusion and of dialysis had to be developed.

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Chapter 4

The science of dialysis: osmosis, diffusion and semipermeable membranes

We must now step back to earlier in the nineteenth century to review what was happening with regard to the eventual removal of these potentially toxic substances. Since the basis for all forms of dialysis is *diffusion*, the development of this field was the second necessary prerequisite for the idea of clinical dialysis to emerge.

Osmosis diffusion and dialysis

The Frenchman René Henri Joachim Dutrochet (1776–1847) (Fig. 4.1) has some claim to be considered as the intellectual 'grandfather' of dialysis [1,2]. Dutrochet was born into a noble family and suffered from a club foot, only later treated by a local healer. He came to medicine late (graduating in 1806) after a period in the navy and then as a soldier in the royalist forces during the French Revolution. He practiced as a country doctor near Vendôme in Touraine on the Loire, outside the mainstream of Parisian medicine (although he was a corresponding member of the Académie des Sciences).

Dutrochet was a naturalist, a follower of Lazzaro Spallanzani (1729–1799), with a wide range of scientific interests. His first work was in phonetics and embryology, and he has some claim to have made the crucial discovery that tissues were made up of cells (which he called 'globules') some time before Schwann and Schleiden, who usually receive credit for this idea—although Dutrochet did not contest their claims when their work was published [3]. However, it was Dutrochet's studies of the transfer of water into and out of these cells and across animal membranes [1,2] which received the most attention, and diverted others from an appreciation of this additional striking advance which underlay his experimental work [3]. Dutrochet introduced the term *osmosis* to describe the passage of water down concentration gradients of salts whilst membranes hindered the passage of solute, and he measured the pressure exerted by this passage of water, which he called osmotic pressure. He proposed also that the kidneys made urine by a process of chemical filtration—14 years before Carl Ludwig's description of filtration through the Malpighian corpuscles or glomeruli. Ludwig, who eventually established this idea in 1842, himself made extensive use of Dutrochet's observations. During the 1830s and 1840s Dutrochet's work on osmosis was extensively discussed both in France and abroad and was widely

Fig. 4.1 René Henri Joachim Du Trochet (later Dutrochet) (1776–1847), son of a French noble dispossessed in the French Revolution, who discovered and named osmosis, and studied the diffusion of solutes into and out of cells, which he described for the first time. He is shown holding his osmometer. (From Schiller J, Schiller T. *Dutrochet* (*Henri du Trochet 1776–1847), le matérialisme mechaniste et la physiologie générale.* Blanchard, Paris, 1975.)

influential, including his firm stand against vitalism and insistence on the unity of vital phenomena in both plants and animals in terms of physics and chemistry.

All studies dealing with the history of dialysis must also pay homage to the genius of the Scottish physical chemist Thomas Graham (1805–1869) (Fig. 4.2), often called the 'father' of clinical dialysis; his life and work are discussed in detail by Gottschalk and Fellner [4,5], and by George [6]. Graham [7–11] was born in 1805 in Glasgow, the son of a prosperous manufacturing weaver, and grandson of a Moderator of the (Presbyterian) Church of Scotland. As a result he was destined for the church and enrolled in the theology course at Glasgow. However, Graham's interests lay elsewhere, and surreptitiously he attended lectures in chemistry, transferring to Edinburgh where chemistry was better developed, but still—so far as his father was concerned—studying theology. Here he published his first papers. Finally his father found out what was happening, and destroyed his chemical apparatus during a visit to Edinburgh in 1828 which led to a prolonged estrangement. For a while he depended upon his mother for secret support. He then became a lecturer in Glasgow after

Fig. 4.2 Thomas Graham (1805–1869) the 'father' of dialysis. (Engraving by C. Cook, after a photograph by Claudet.)

which he was appointed to University College London in 1837, where most of his best known work was done; inheritance of an estate in Scotland eased his financial position at last. In 1855 he succeeded Sir John Herschel as Master of the Royal Mint, a post he held until his death.

Graham was a solitary, modest man, who never married and had few close friends, perhaps because he communicated poorly—he had difficulty in keeping his classes' attention and was described by one pupil as having as a young man a 'quiet, rather stiff and hesitating manner which he never lost' [11]. In addition his health was poor throughout his life, and he turned down the Presidency of the Royal Society of London because of this. Nevertheless he was well known nationally and internationally, being a close friend of the great Justus von Liebig (1803–1873), and after his death a statue was erected in Glasgow (Fig. 4.3).

Graham took three giant steps in thinking about what we call diffusion: first, he evolved the laws of diffusion of gases which now bear his name [12,13] which state that the rate of diffusion of a gas is inversely proportional to the square root of its molecular weight; second, he investigated the nature of osmotic force [14]; and finally in a massive 50-page paper he described the separation of substances across mem-

Fig. 4.3 The statue of Graham in George Square, Glasgow—a place of pilgrimage for students of dialysis including Willem Kolff, as in this photograph taken by Dr Marjorie Allison of Glasgow. As is usual in Glasgow, it was raining. (From [4].)

branes, re-defining the word *dialysis* to describe this process [15]. Graham's realization that Dutrochet's osmosis was 'the conversion of chemical affinity into mechanical power' remains an exact description. That the essential basis of a clinical technique was made by one without any clinical interest or training should not surprise us: it is so in almost all areas of clinical medicine except for the most empiric. By 1861, Graham [15] had distinguished what he named 'crystalloids' (such as sugar) from 'colloids' (both of which terms he introduced), such as gum arabic, from their property of being retained by, or passing through, what he termed 'semi-permeable' membranes such as writing paper impregnated with starch—the first ever dialysis membrane (Fig. 4.4). Again with great clarity of vision and expression he stated the crucial event: 'molecules are moved by the force of diffusion'.

Although Graham was a chemist and not a physiologist, he noted as early as 1854 that 'chemical osmose appears to be an agency particularly well adapted to take part in the animal economy'. Later he made the observation, crucial in determining that in the future investigators would think of using dialysis for uraemia, that urea could be dialysed through semipermeable membranes [15]:

> Half a litre of urine, dialysed for twenty-four hours, gave its crystalloid constituents to the external water. The latter, evaporated by a water-bath, yielded a white saline mass. From this mass urea was extracted by alcohol in so pure a condition as to appear in crystalline tufts upon the evaporation of the alcohol.

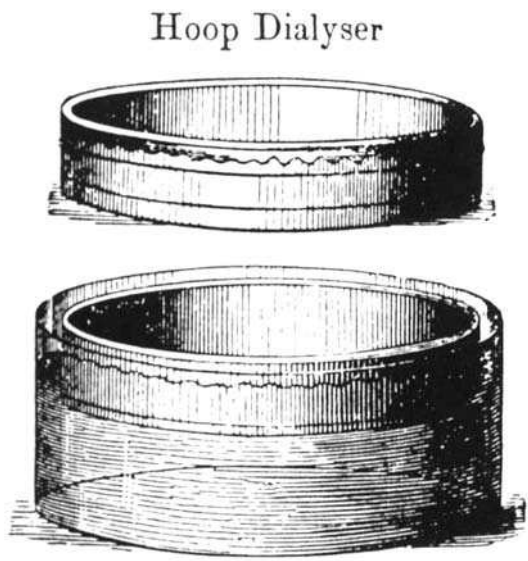

Fig. 4.4 One of Graham's many dialysis apparatuses. This one is based on a simple hoop, with the membrane separating two solutions. (From [14].)

The history of dialysis is but one of many areas of medicine demonstrating the application of science to a clinical problem. One can assert with confidence that the *basic science* underlying clinical dialysis was virtually completed with Graham and Piorry's work around 1850–1860, together with its molecular and mathematical refinement by the Dutchman Jacobus Henricus Van't Hoff (1852–1911) in 1887 [16]. The following 100 years were taken up with its *application*—a matter of imagination, technology and invention—but not of new science. This does not imply that the many talented individuals who brought dialysis to clinical fruition were not clinical scientists: only that they had no need to generalize new principles, except perhaps convective transport (see below). What they *did* require was the imagination to see the potential utility of the science outlined by the French school, by Christison and above all by Graham.

Dialysis membranes in the laboratory

Although the history of *clinical* dialysis appears a blank for nearly half a century following Graham's death, the technique and science of dialysis was much discussed in the years immediately following Graham's work, and came into widespread use in laboratories for separation and purification by the turn of the century. During this time many membranes were tried in the laboratory for dialysis: in 1886 Zott [17] compared no less than 15 different membranes, concluding that gold-beater's skin (the parietal peritoneum of calves or lambs) was the best. However, another material which was to have a huge influence on the early application of dialysis was at hand, one not employed by Graham or tested by Zott: *collodion*.

Fig. 4.5 Carl Friedrich Schönbein (1799–1868) of Basel, who developed guncotton and made collodion, thus making early dialysis possible. (From [19] with permission.)

'Collodion' was the name first applied by the famous Swiss alchemist, chemist and phsycian Paracelsus (1493–1541) to substances like glue (from the Greek κόλλα), but by the middle of the nineteenth century it was more usually applied to solutions of cellulose salts in organic solvents, such as alcohol or ether mixtures. Cellulose trinitrate (trinitrocellulose, gun cotton or Schiessbaumwolle, from its explosive properties on igniting) was first synthesized by dissolving cotton in nitric acid alone by H. Branconnot in France in 1833 [18]. It was studied further by Théophile Jean-Jacques Pelouze (1807–1867) in 1838, who has been credited with its discovery [19]. However, it was the accidental use of a mixture of nitric and sulphuric acids to solubilize cotton whilst nitrating it completely, by the Swabian Carl Friedrich Schönbein (1799–1868) in 1845 (Fig. 4.5) [19], which captured immediate attention worldwide. Working in Basel after a period teaching in Epsom, England and as professor in Erlangen, it is said he used his wife's apron to wipe up such a mixture of acids, and the accidental result was gun cotton. Schönbein patented the material and it was used widely as an explosive in mining, including, later in the century, Alfred Nobel's famous 'dynamite'.

However, Schönbein was responsible alone for the further discovery that the incompletely nitrated *di*nitrocellulose, when dissolved in a mixture of alcohol and ether, could be painted on to surfaces—including skin—and would dry to leave an occlusive film. It was used as a surgical dressing in this way from 1848 [19]. It was extensively used also by pioneer photographers in the wet collodion process invented in 1851 by the Englishman Frederick Scott Archer (1813–1857), which for the first time permitted multiple copies to be made from a single negative. Nitrate remained the stock used for cinematography until about 1935, when it was gradually replaced by less flammable and more stable cellulose products.

As early as the 1850s, the great German physiologist Aldolf Fick (1829–1901) was amongst the first to examine diffusion though collodion sheets [20], describing the molar diffusion flux of substances, after pharmacologist Rudolf Buchheim had described perhaps the first work in this area [21]. Collodion could be easily

manufactured into tubes using wide glass tubing as the supporting material, and turned into bags by tying the ends, such as those used by Schumacher in 1860, who introduced the term 'membrane diffusion' [18,22]. Later, in an important comparative paper Lawrence Bigelow and Adelaide Gemberling of Michigan concluded in 1907 [23] that of the many membranes available although gold-beater's skin was best, collodion was the most practical membrane for dialysis. They analysed the diffusion properties of collodion prepared in different ways in detail. This paper must surely have been known to those who were to first attempt *in vivo* dialysis, only 6 years later.

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concentration in one region of the liquid or gas, the random movement of the components of the mixture will ensure that eventually the concentration will be the same everywhere within it. Thus if blood is exposed to a solution with a lower concentration of any solute dissolved in it—say urea—the tendency will be for the urea to diffuse to the solution with a lower concentration. Similarly, if there is a higher concentration of (say) glucose in the dialysis solution, then it will tend to diffuse into the blood plasma. The interposition of a membrane which allows the passage of such small molecules, but denies passage to much larger ones such as proteins or the cells of the blood, creates a situation in which dialysis can take place. An additional factor is how much—or how little—the membrane used obstructs the passage of the small molecules. Most membranes allow smaller molecules to pass (but less rapidly than water), and progressively larger molecules pass more slowly, until a cut-off is reached when they do not pass at all. These characteristics describe the permeability of the membrane (see Chapter 17, Fig. 17.2).

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Chapter 5

Anticoagulation and extracorporeal circuits: the first haemodialysis

The beginnings of anticoagulation

Blood is a difficult substance to work with: on exposure to almost any surface available until the mid-twentieth century, it clotted and separated serum from a fibrin-cellular coagulum. Thus, even *in vitro* dialysis from untreated whole blood was impossible, and early attempts at extracorporeal perfusion inevitably failed [1]. However, Prévost and Dumas had shown in 1821 that blood from which the clotting protein fibrin had been removed by whisking did not coagulate[2], and mechanical perfusion of organs (including the kidney) was carried out successfully using defibrinated blood by the mid century [3]. That dark venous blood became redder and arterialized when shaken was known, and the principle of oxygenating blood by agitation was established; kidneys perfused using oxygenated blood were studied by Bunge and Johann Schmiedeberg (1838–1921) in 1876 in Strassburg [4], now part of Germany following the Franco-Prussian war of 1870. These perfusion systems were perfected further by Jacoby, a pupil of Schmiedeberg's, during the 1890s.

Meanwhile it had been known for centuries that leeches secreted a substance which interfered with blood clotting and allowed them to feed for long periods, and in 1884 John B. Haycraft, a professor of physiology in a college in Birmingham, England, extracted anticoagulant activity from the heads and gullets of leeches [5,6]:

> The blood flowing from a leech bite is not rapidly stopped, often flowing for upwards of an hour after the animal has been removed. The blood within the body of the creature remains fluid for an indefinite time … probably the leech secretes some ferment-containing juice which antagonizes the blood ferment, preventing coagulation … in order to investigate its action on the blood, a salt solution extract of leech was obtained.

Together with Schmiedeberg he was able to show this extract was active also *in vivo*. However, it was only in 1903 that Friedrich Franz prepared it in moderate purity [7]—interestingly using dialysis as part of the purification process. The name *hirudin* (from *hirudo medicinalis*, the medicinal leech) was applied to the crude extract, again by Jacoby who used it for his organ perfusion experiments [8]. A major problem remained: many batches of hirudin evoked toxic reactions when injected into animals or man, so that whilst it could be used in circuits in the laboratory, its utility was limited; although it became popular as a treatment of so-called toxaemia of pregnancy in Germany around 1909 [6], and by this time was commercially available in that country. Nevertheless, without hirudin the next steps in the development of clinical dialysis could not have taken place.

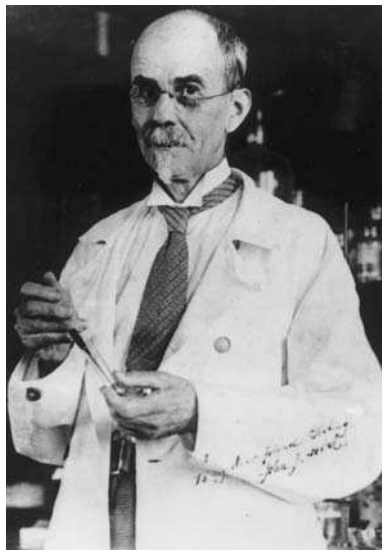
Even before hirudin became available, during the final years of the nineteenth century, several workers (of whom probably the first was B.W. Richardson in London in 1889 [9]) dialysed *in vitro* either whole blood defibrinated by whisking, or separated serum. Now that by 1910 suitable membranes were available in the form of collodion, anticoagulation of the blood whilst in the dialysing apparatus was possible, and the technology for extracorporeal circuits was familiar. In retrospect one can see that soon after this time someone would hit upon the idea of *in vivo* dialysis of blood. The individual who thought of this first and applied the idea was John Jacob Abel.

In vivo dialysis in animals

Despite much information on his laboratory and its aims it is not clear how Abel (1857–1938) (Fig. 5.1a) came to think of doing *in vivo* dialysis of blood, or what his precise purpose was in performing his experiments [10]. However, he must have been aware of the extensive literature on dialysis as a laboratory tool for the preparation of substances from complex solutions. The work of Emil Aberhalden (1877–1950), a Swiss physiologist working in Halle, Germany, on the use of dialysis to separate substances putatively found only during pregnancy [10] and published from 1912 onwards may have been the stimulus. Subsequent accounts suggest that the idea that he and his team might study dialysis *in vivo* arose during regular lunchtime 'brainstorming' discussions in Abel's laboratory during the fall of 1912, at which Eli K. Marshall was also present [11]: 'small cylinders rolled from the luncheon bread were used to illustrate the apparatus'. The first experiments were done using a two-tube apparatus in a rabbit on 10 November of that year.

Several biographical articles are available on Abel's life and contribution to medical science [11–18] including a multipart recollection of his life and work by colleagues in his hospital journal [11,16–19]. Abel was of German ancestry, from the Rhine valley, and was born on 1857 on a farm in Ohio, near the town of Cleveland. He went to the University of Michigan, but only graduated as a PhB in 1883 at the age of 26 because first he served as principal of the high school in LaPorte, Indiana for 4 years due to lack of money, during which time he married Mary Hinman, another teacher. After a years' postgraduate work under the physiologist Newell Martin at Johns Hopkins, he spent 7 years travelling and studying in Germany, Austria and Switzerland, receiving his DM from Strassburg in 1888, even though he was a scientist and not a clinician. This extended period of study was funded by his and his wife's joint savings, and he encountered most of the great clinical and scientific German researchers of the period: Carl Ludwig, with whom he spent some time, became his idol and Schmiedeberg in Strassburg prompted his interest in pharmacology.

On his return to Michigan in 1892, he was appointed Professor of Materia Medica there, but was recruited by the indefatigable Sir William Osler only a year later to the new post at Johns Hopkins, the pair having met on a transatlantic boat journey. In Baltimore, Abel remained for the rest of his career as Professor of Pharmacology, and until 1908 as Professor of Biochemistry as well. At the Hopkins he became a figure of awe for a generation of students and colleagues, always referred to as 'the professor' by



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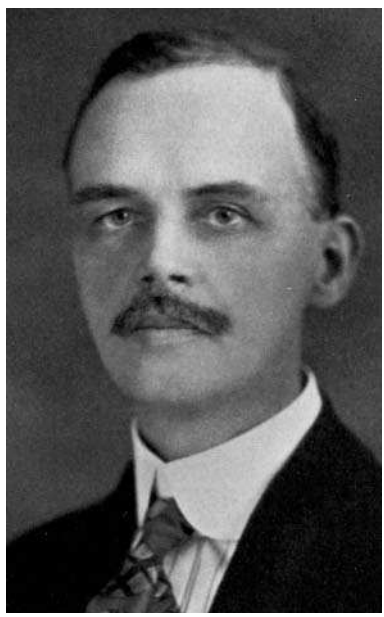


(c)

(d)

Fig. 5.1 (a) John Jacob Abel (1857–1938) in later years; (b) Leonard Rowntree (1883–1959); (c) Bernard Turner (1871–1945)) as a young man, and (d) in later years. With Abel as leader, this team conceived and—with great skill—built the first dialyser for use *in vivo*. ((a) courtesy of the Alan Mason Chesney Archives, Johns Hopkins University; (b) courtesy of the New York Academy of Medicine; (c, d) courtesy of the library of the University of Indiana.)

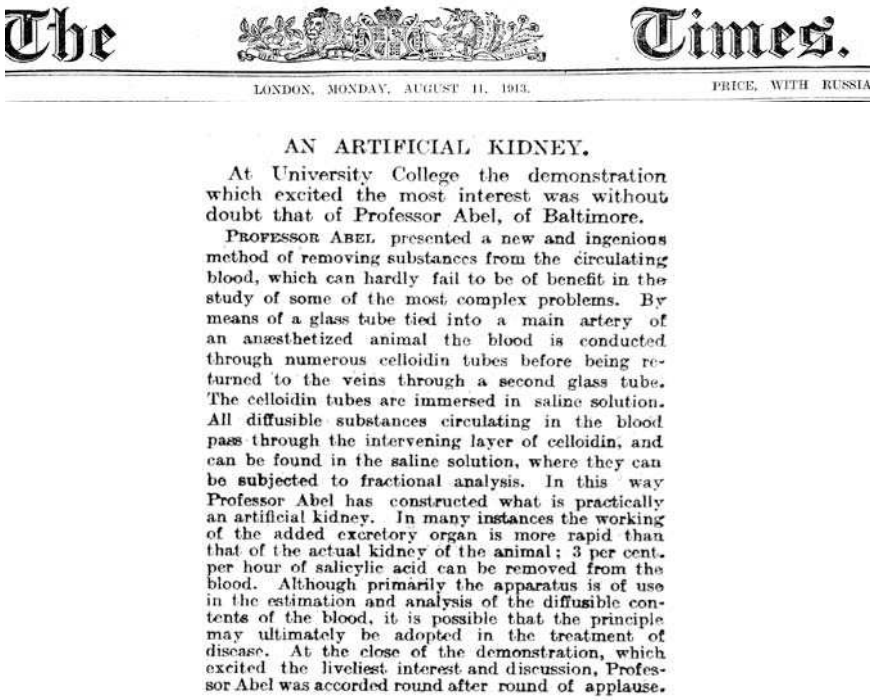
the many who worked under his supervision. Almost all pictures of him depict the elderly grave professor of the period after the First World War, and often wearing the surgical skull cap, long gown and rubber apron he employed during his laboratory sessions. Interestingly, Rowntree (see below) reveals that Abel had one glass eye. He was neat and trim, tall and always wore a goatee beard. Despite the awe he engendered, Abel evoked great personal loyalty and affection in his associates. He modelled his behavior on the German greats with whom he had worked, employing a personal '*diener*' to do his laboratory work; in 1913 this was a man called Charlie Kamphaus, who played a major role in the construction and running of the dialysis apparatus. Abel's other contributions are too numerous to list here, but an abiding interest in hormones was a feature: he very closely missed being the first to isolate adrenaline in 1897, whilst in 1925 he obtained and stardardized crystalline insulin for the first time with E.M.K. Geiling. He played a major role in shaping American science by founding a number of journals, including the *Journal of Experimental Medicine*, the *Journal of Biological Chemistry* and the *Journal of Pharmacology and Experimental Therapeutics*. In 1932 he retired, and died at the age of 81, with his mind still sharp and critical, on 28 May 1938.

Recently, Charles George [19] has started what is likely to be a prolonged debate by the provocative suggestion that at no time during the experiments of 1912–1914 on dialysis did Abel actually intend to treat renal failure. This is despite the broad agenda outlined right at the beginning of the first classic paper of 1913 'On the removal of diffusible substances from the circulating blood by means of dialysis' [20], a brief and general record of his presentation to the meeting of the American College of Physicians in Washington that year:

> There are numerous toxic states in which the eliminating organs of the body, more especially the kidneys, are incapable of removing from the body at an adequate rate the natural or unnatural substances whose accumulation is detrimental to life. In the hope of providing a substitute for such emergencies … a method has been devised by which the blood of a living animal may be submitted to dialysis outside the body … the process may be called 'vividiffusion'.

Despite George's well-founded objections, Abel and his colleagues must be given credit, first, for thinking of doing *in vivo* dialysis of blood; and second, for the considerable technical achievement of designing and building an apparatus to carry this out. However, George makes a convincing case [10,19], from detailed examination of Abel's laboratory notebooks and letters as well as published accounts, that Abel's interest throughout was to use the *in vivo* dialysis either to extract exogenous toxic substances (such as salicylate, phenolsulphthalein and iodide), or to purify and identify endogenous amino acids and other nitrogenous substances in the dialysate: that is, to produce what Rowntree later called '*an artificial urine*'. Certainly, he showed no interest whatsoever in the urea present in the material, which he treated as an obstacle, removing it with urease before further analysis; in only one experiment is the amount of urea removed recorded: 20 g. Nor is uraemia mentioned as one of the 'toxic states' to be relieved by dialysis.

It is possible that at least some of the clinical insights and possible future relevance to renal failure of their work originated with the second author of their papers,



The Times.

LONDON, MONDAY, AUGUST 11, 1913. PRICE, WITH RUSSIA

AN ARTIFICIAL KIDNEY.

At University College the demonstration which excited the most interest was without doubt that of Professor Abel, of Baltimore.

PROFESSOR ABEL presented a new and ingenious method of removing substances from the circulating blood, which can hardly fail to be of benefit in the study of some of the most complex problems. By means of a glass tube tied into a main artery of an anæsthetized animal the blood is conducted through numerous celloidin tubes before being returned to the veins through a second glass tube. The celloidin tubes are immersed in saline solution. All diffusible substances circulating in the blood pass through the intervening layer of celloidin, and can be found in the saline solution, where they can be subjected to fractional analysis. In this way Professor Abel has constructed what is practically an artificial kidney. In many instances the working of the added excretory organ is more rapid than that of the actual kidney of the animal; 3 per cent. per hour of salicylic acid can be removed from the blood. Although primarily the apparatus is of use in the estimation and analysis of the diffusible contents of the blood, it is possible that the principle may ultimately be adopted in the treatment of disease. At the close of the demonstration, which excited the liveliest interest and discussion, Professor Abel was accorded round after round of applause.

Fig. 5.2 The article in the *Times* of London, composed by an unknown hand, which coined the term 'artificial kidney'.

Leonard George Rowntree (1883–1959) (Fig. 5.2b), who has received insufficient attention from historians of nephrology hitherto. Rowntree [21,22] was born in London, Ontario, the son of a successful businessman, and in 1958 he wrote an autobiography permeated with what seems today to be an extraordinary optimism [21]. After graduation from Western Ontario in 1905, he moved in 1906 to join his uncle (who had graduated in Philadelphia) in general practice in Camden, New Jersey, just across the Delaware river from that town, where he worked as well in hospital outpatient clinics. He appears to have been a successful and well-liked practitioner, and to have enjoyed life, but he became restless and stayed there only a year, having been recruited to the Johns Hopkins, again by Sir William Osler, after the latter gave a talk in Philadelphia attended by Rowntree during a visit to the United States from Oxford. Osler suggested he come to the Hopkins and work in an unpaid capacity for Abel, which he did, supplementing his income by summer periods of consulting in Camden.

After a year's laboratory training he worked under Abel's supervision on phenolsulphthalein as a purgative in 1908–1909, and then with J.T. Geraghty introduced a renal function test based upon its secretion [23,24] which remained in use worldwide for some 40 years thereafter. He left Abel's department in 1914 to take up a clinical post which allowed him to marry. Later in 1915 with Norman Keith (1885–1976) as

lead author, he co-described the first measurement of blood volume using a dye–dilution method [25]. He left Baltimore altogether in 1916 for Minnesota, then after a period of military service went to the Mayo Clinic in 1920, where he remained for 11 years and published more than 100 papers—a very large number for the period. These included, in 1923, the use of iodine to visualize the renal tract radiographically [26] and also the description of the first lumbar sympathectomies for the treatment of hypertension [27]. He published also one of the first papers on the histology of renal manifestations of systemic lupus [28] and studied the new anticoagulant heparin in an extracorporeal circuit (see below). Finally, he moved back to Philadelphia in 1932 to lighten his workload, serving during the Second World War as head of the national board on health of inductees. He survived to witness one of the early dialyses in humans for salicylate poisoning at Georgetown in 1955 [29].

The third member of the trio, Benjamin Bernard Turner (1871—1945) (Fig. 5.1c, d) has remained almost unknown [30–34]. He was a biochemist who (like Abel) was German educated (including in Strassburg where he may have encountered hirudin), taking his PhD in Goettingen in 1899 in physical chemistry (entitled *Über die Dielektrizitätskonstanten reiner Flussigkeiten*) under the direction of Nobel-prize winning Hermann Walther Nernst (1864–1941) whose eponymous equation is known to all nephrologists. However, Turner was of English origin, being born of missionary parents in Hong Kong (his father, F. Storrs Turner, had been involved in the so-called 'Boxer rebellion' of 1900) who nevertheless fostered an interest in science in all their children, giving scientific apparatus as Christmas presents for the children's joint laboratory; his brother became a paediatrician, emigrating to Brisbane, Australia in 1888. Turner was an excellent linguist, speaking six languages fluently with knowledge of another four including Sanskrit and ancient Egyptian, and learned to speak Polish in retirement during a visit to that country. His early education was in England, and he took his initial science degree in London in 1894. He emigrated to a post in an agricultural college in Connecticut in 1900, moving on rapidly to Cornell and then to the University of Missouri in 1902. However, he maintained his European connections, spending the summer of 1904 in Strassburg and 1910–1911 in Leiden, having moved to set up a physical chemistry laboratory at the Johns Hopkins in 1907; later he transferred to Abel's department.

Rowntree [21] credits him, amongst other things, with the glass work on the vividiffusion apparatus—a considerable feat when one looks at the manifold (Figure 5.4)—whilst Rowntree himself made the leech extracts and the collodion tubing, Abel performing the chemical analyses and supervising the programme. Turner went to Indiana as Professor of Pharmacology and Biochemistry in 1915, retiring in 1933. A lifelong bachelor, he lived on campus in quarters [33]:

> which were quite beyond description. His room was piled to the ceiling with books, papers and periodicals. He ate when and where he thought of eating, and in spite of the fact that he knew more about nutrition than the rest of the faculty put together, he ate very badly … his clothing was bought without regard to style or fit, and worn until it was threadbare. His hair he cut himself, and it was pretty likely to be badly notched up … Never have we known a better man—or a more impractical one.

He published little whilst at Indiana, where he was known as 'bye the bye Turner' after his initials, and the habit of using this in his speech, and to the students as a 'walking encyclopaedia'. Instead he devoted himself to building up the library, where his knowledge of languages was a strength [33].

This talented trio took their apparatus (described below) to Europe and demonstrated the dialysis of salicylate from the blood of a living animal at international medical conferences in London and in Gronigen in 1913, which aroused considerable public interest, with many press reports in newspapers all over the world as well as in the medical journals [10,19]. At first, in some ways the technically more accurate term of 'artificial glomerulus' was used in the *British Medical Journal* [35,36], but in the London *Times* of 11 August 1913, as part of their coverage of the conference, running to several pages, an article appeared under the heading 'An artificial kidney' (Fig. 5.2), noting that 'it is possible that the principle may ultimately be adopted in the treatment of disease'.

Thus, the most resonant term in all nephrology was coined, not by a physician or scientist working in the field, but by an unknown British press copy-writer almost 90 years ago. Nevertheless, most of the reportage revolved around the diagnosis and treatment of poisoning. However, following a further demonstration to the American Societies of Experimental Biology on 30 December 1913, the *New York World* of 31 December quoted [10]:

> Scientists who witnessed the demonstration showed enthusiasm about the opportunity opened by the Baltimore men. 'If this method of diffusion removes urea from the blood' said one 'it can be used as a cure for uremia'.

Newspapers worldwide mentioned their work, but usually in terms of removing 'poisons' from the blood, and without mention of renal failure specifically. Although Abel kept all these many cuttings in his files [10], and received a number of letters asking for dialysis treatment of renal disease, none of the three *subsequent* papers describing their technique and results in detail allude to dialysis of urea, or to the treatment of renal failure at any point. As George has suggested [10,19] it seems that Abel's several *later* references from 1920–1930 to this possible application of their work [10,19,29,37] were additions engendered not only by this publicity, but also in the light of subsequent work by Necheles and then Haas, rather than integral to the project at the time. Even in his Mellon lecture of 1915, well after all the publicity, Abel makes no reference to the treatment of renal failure by dialysis, even though he specifically refers to this as a goal with regard to his new interest in 'plasmaphaeresis' [38]. Thus, despite subsequent canonization, Abel, Rowntree and Turner did *not* describe dialysis for the purpose of treating uraemia, but for the purpose of elaborating an 'artificial urine', which could then be studied chemically. If any one of the trio had that idea to begin with it would in all probability have been the clinician Rowntree, even though he was the most junior. However, he does not make this point even retrospectively in his autobiography, written when dialysis (at least for acute renal failure) was already a clinical reality [21], and after he had witnessed personally the removal of salicylate from man using dialysis, as he and his colleagues had done in dogs in 1913 [29].

What was this 1912–1914 vividiffusion apparatus like (Figs 5.3 and 5.4) [19,29,39,40]? Some components of the apparatus are still available in the library collection at the Johns Hopkins Hospital along with Abel's laboratory records and correspondence. The hollow dialysis tubes were made of collodion, and detailed instructions for its optimal preparation for dialysis are given [39]. Each tube was about 8 mm in diameter and 40 cm in length (about 0.32 m^2 in total), and connected at either end by a glass manifold to receive and return the blood contained within the tubes. The whole mass of tubes was mounted inside a glass cylinder, within which

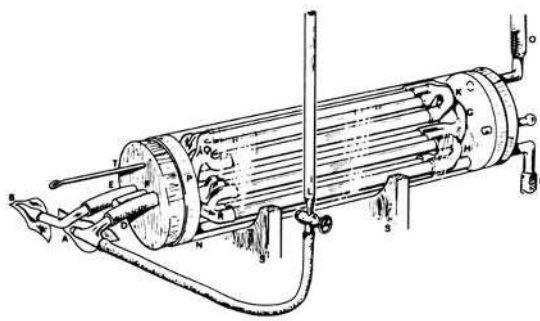


Fig. 5.3 Abel, Rowntree and Turner's 'vividiffusion' apparatus. (From [39]. See text for discussion.)

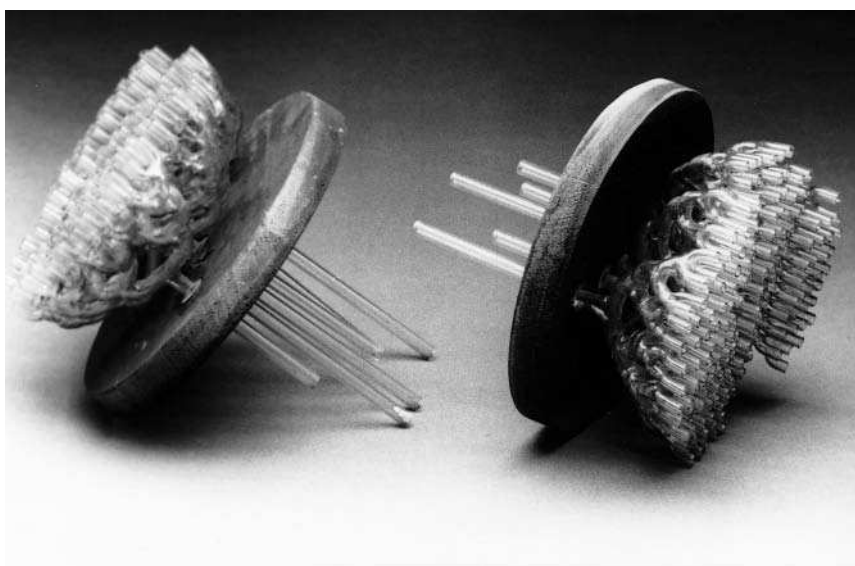


Fig. 5.4 The glass manifold of the vividiffusion apparatus, made by Bernard Turner—clearly a very skilled glass-blower! (Courtesy of Alan Mason Chesney Archives, Johns Hopkins University.)

the dialysate circulated. The system was pumpless, using the force of the heart to drive the blood through the extracorporeal circuit from carotid artery to superior vena cava.

Although Abel and his colleagues probably had only a vague idea of the diffusion characteristics of their membranes, they realized virtually all the important parameters of the dialyser in these pioneer experiments, maximizing the surface area available for dialysis as best they could, and noting [40], 'very small tubes would undoubtedly prove valuable when the necessary time and trouble are not prohibitive', thus predicting the modern hollow-fibre dialyser. They noted also that flattening the tubes improved the efficiency of dialysis; the only points they failed to make relate to the dialysate. That agitation of the dialysate improved the exchange of solute had been noted *in vitro* in 1909 [19], but the observation was made again almost immediately *in vivo* by C.L. von Hess and Hugh McGuigan in Chicago in 1914 [41], who used their own version of the Abel–Rowntree dialyser to show that blood sugar was freely dialysable, and thus not protein bound. These authors also used pulsatile arterial blood access using a diaphragm to minimize clotting, with such success that their apparatus usually required no anticoagulation. However, Abel and his colleagues used static dialysate, not a countercurrent flowing system, which is the most efficient mode—probably because their main goal was not so much efficient removal of material from the blood stream, but in order to minimize the volume of dialysate for subsequent chemical and other analyses.

Abel and his colleagues had major problems with the hirudin they used, as George has reviewed in detail [6,19], but which does not appear in their published papers. Febrile reactions led to them preparing their own hirudin, a job carried out by Rowntree, and the process was described in detail in a later paper. This makes all the more puzzling Abel's later justification for abandoning work with the 'artificial kidney' in 1915—especially the crucial transfer of the work to human subjects—on the basis of the non-availability of good hirudin, as George has pointed out [6,10,19]. The best European leeches were available from Hungary and Abel imported his leeches from there. The United States then entered the World War: the leeches were declared to be of 'enemy origin', and were destroyed in transit in Denmark. In a letter to Leonard Rowntree, now at the Mayo Clinic, Abel wrote in 1930, 'I could not help thinking how unfortunate it was that our work was stopped by the World War when we were unable to obtain the supply of leeches' and goes on to suggest that Rowntree start a programme in his clinical service to investigate the possibility of treating patients suffering from the terminal phases of chronic nephritis using dialysis, with relief of symptoms and possible extension of life:

> 'I have always had the belief, and I recall you agree with me, that something could be done by this method in cases of acute mercurial poisoning [i.e. with acute renal failure]. If the blood could be washed every day, or every other day, in these cases at the time when they become stuperous [sic] and unconscious, they might recover. The kidney, I understand from the pathologists, has a great regenerative capacity.

The same theme emerges from the soundtrack of a film made by Abel ay about the same time, in which he reviews his work for the camera [37]. Of course by this time Haas had already dialysed a number of human subjects (see below) and Abel men-

tions this in his commentary in the film. As late as 1924, in a letter to Heinrich Necheles [10] (see Chapter 6), he was still blaming the lack of good leeches on this inability to help a young colleague treat a patient with acute renal failure from mercury chloride poisoning, despite directing Necheles' attention on how to prepare it from one of their 1914 papers!

It seems much more likely that Abel abandoned dialysis for the simple reason that the two people who had made the work possible had left him: Rowntree to a clinical post at Hopkins in 1914 and then completely for Minnesota in 1916, and Turner in 1915 to Indiana. Without their expertise, even with his now experienced *diener*, Abel would have been unable to construct and use the intricate manifolds necessary for their design—although Hess and McGuigan had shown already that a single long collodion tube could be used, provided turbulent flow and a high flow rate of dialysate were obtained.

Instead, Abel changed his interest briefly to plasma exchange, or '*plasmaphaeresis*' as he called it [42]. Here there is no doubt whatever that his goal in these experiments was the relief of uraemia, and after successful dog experiments a single unfortunate human subject was given the treatment in 1915, although only 400 ml were exchanged, probably because of the severe reaction to the hirudin anticoagulant. A colleague's detailed description of this occasion demonstrates just how little contact with—or understanding of—clinical medicine Abel possessed [15].

It seems doubtful, moreover, whether in 1913–1915 hirudin could have been obtained of sufficient purity and free of toxic reactions to allow its use in humans at the doses required, despite its prior use in Germany for toxaemia of pregnancy as mentioned above. The blunt fact is that the great majority of their dogs died during the experiments for one reason or another, probably in most cases from toxicity of the hirudin—a fact which did not appear in any of their published papers [10,19]. However, they did construct one vividiffusion apparatus with 192 tubes which must have had a surface area large enough to dialyse a human, if one of 32 tubes could dialyse non-protein nitrogen successfully out of a 20 kg dog. In the end, Abel spent the next 10 or more years on his main life-long interest—hormones in the blood, in particular, during the early 1920s, insulin, which he succeeded in crystallizing for the first time.

Notes and references

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Chapter 6

The search for better dialysis membranes: the peritoneum and the beginnings of peritoneal dialysis

For a while Europe, and then the whole world, was occupied by the First World War. Nevertheless in the United States a further paper—besides that of Hess and McGuigan—employing *in vivo* dialysis appeared: Alice Rhode, a pupil of Abel's, used *in vivo* dialysis to quantify ammonia in the blood [1]. After the end of the war this work in Baltimore continued to attract a good deal of attention. Clearly there was the possibility of a useful treatment, but the technical problems were formidable. Apart from the hirudin problem, if dialysis was ever to become successful in humans, another difficulty of the Abel–Rowntree–Turner dialyser had to be resolved: the relative fragility of the collodion membranes, and the tedium of their manufacture.

The search for better dialysis membranes

In 1920 a chemist in the Hahnemann Medical College of Chicago, G.R. Love, designed a 'vividiffusion apparatus with intestinal membranes' using the much tougher dried chicken intestinal membrane as ready-made tubing [2], but this appears not to have been followed up. As in Abel's work, the purpose seems to have been 'study of the substances constituting normal blood' without any therapeutic implication. Love describes how to make the membranes semipermeable and thus impermeable to colloids, using treatment either with albumin and sodium chloride or picric acid. A year later, Van der Hyde and Morse in West Virginia used collodion precipitated on to fish bladder as a dialysis membrane, to make it less fragile and re-usable [3]. There is no record this was ever used, however. The only further work using *in vivo* dialysis during the next decade that I have been able to identify was that of Greene and Power in 1931 [4], who studied the transfer of electrolytes from blood into the dialysate.

For the next few years, the focus of work on dialysis moved to Germany, first of all through the work of Heinrich Necheles (1897–1979) (Fig. 6.1), who was the first individual who quite clearly set out to treat uraemia by dialysis. Necheles [5] was born into a Jewish family in Hamburg, the son of a merchant, and left there after his school years to study medicine in Berlin in 1915. His studies were interrupted by a period of war service from 1916 to 1919, and after further studies in Kiel and Freiburg as well as

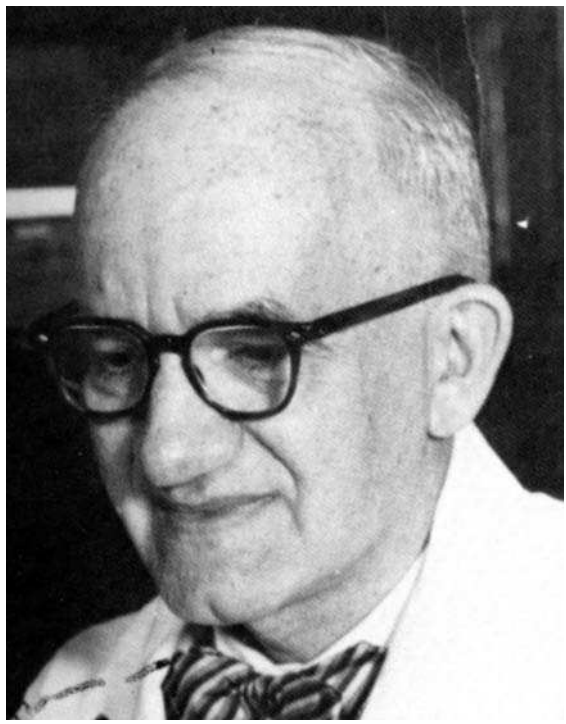


Fig. 6.1 Heinrich Necheles (1897–1979). Like Haas, Necheles survived to see his work come to clinical fruition during the 1950s and beyond. (Courtesy of Gattis McCullough, from: McBride PT. *The genesis of the artificial kidney*, 2nd edn. Baxter Healthcare, Chicago, 1987.)

Hamburg, he graduated in 1922. Remaining in his home town, he did two clinical years before moving full-time into physiology in 1924. In 1923 he published his paper on dialysis [7,8], which formed the subject of his MD dissertation awarded in the same year. His physiological studies were supported by the Rockefeller Foundation, which in 1925 funded him to go to Beijing, where he spent 4 years before going to the University of Chicago, still in physiology, later transferring to the department of gastroenterology at the Michael Reese Hospital. Regular collaboration with his alma mater was interrupted by the Nazis, and he remained in the United States, continuing to publish in physiology until 1962.

Necheles must have the credit for having first used a dialysis apparatus with the clear intention of relieving uraemia, and dissatisfied with collodion he tried a different dialysis membrane. He wrote to Abel [9–11] for technical help with hirudin, and was reassured by Abel in his reply that he and his colleagues had always intended to treat patients as Necheles proposed [10]. Necheles returned to earlier work and used gold-beater's skin (a commercial preparation of visceral peritoneum from calves' abdomen) as his dialysis membrane, in what would now be recognized as several flat-bed dialysers with membrane supports mounted in series (Fig. 6.2).

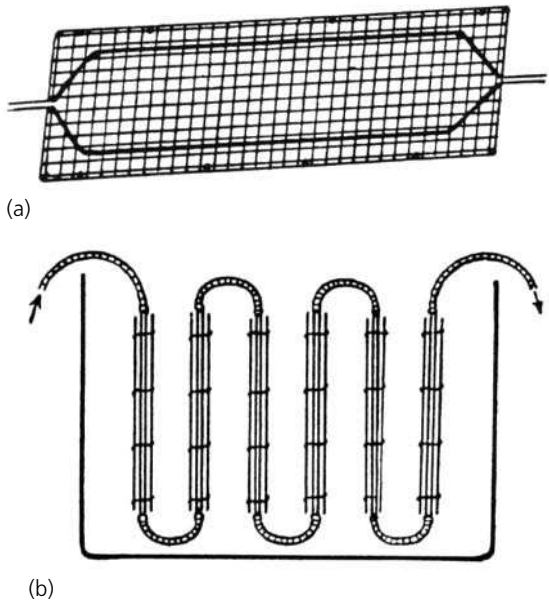


Fig. 6.2 Necheles' dialyser of 1923: (a) the pairs of dialysis membranes maintained flat using a support, and (b) several such dialysers connected in series to make a dialyser. This design presaged the flat-plate dialysers of the 1960s to 1980s. (From [7].)

He dialysed dogs rendered uraemic by nephrectomy, successfully using this apparatus ' in order to reduce the substances remaining in the body in the case of uraemia which are increasingly poisonous', with improvement in their uraemia. Again hirudin was used as anticoagulant.

The use of peritoneal membrane *in situ* for dialysis

Necheles used the peritoneal membrane *ex vivo* for dialysis. At about the same time as Necheles' work, also in Germany but at the University of Würtzburg, a senior medical resident called Georg Ganter was exploiting the human peritoneum *in situ* as a dialysing membrane for the first time, and Necheles learned of his experiments. To understand this development, however, we need to retrace our steps a little.

The peritoneal cavity had been known since Egyptian times. Well before any concept of diffusion or exchange had developed, the idea of peritoneal lavage arose as a treatment for the collection of fluid within the abdomen in liver and other diseases—ascites. Tapping ascites to relieve the pressure must have been occurring for centuries, even though the risks of infection and circulatory collapse must have been high. The early eighteenth century paper of Chistopher Warrick, a surgeon from Truro in Cornwall, England [12], and the comment on it by the Reverend Stephen Hales [13], rector of Teddington, author of *Hydrostaticks* and the first to measure blood pressure, have been much quoted and discussed in the context of dialysis since attention was drawn to them by David Earle [14]. This is because Hales' paper (Fig. 6.3) introduced

IV. *A Method of conveying* Liquors *into the* Abdomen *during the Operation of* Tapping; *propoſed by the Reverend* Stephen Hales, *D. D. and F. R. S. on Occaſion of the preceding Paper; communicated in a Letter to* Cromwell Mortimer, *M. D. Secr. R. S.*

S I R, *Feb.* 22. 1743-4.

Read Feb. 23. 1743-4. IT occurred to me, on your reading, *Thurſday* laſt, before the Society, the Caſe of the Woman at *Truro* in *Cornwall*, who was cured of a Dropſy, by injecting into the *Abdomen* *Briſtol* Water and *Cohore* Wine, after having drawn off a good Quantity of the dropſical *Lympha*; that, in caſe of further Trial, that, or any other Liquor, ſhall be found effectual to the Purpoſe, it might be more commodiouſly injected in the following Manner; *viz.*

By having Two *Trochars* fixed at the ſame time, one on each Side of the Belly; one of them having a Communication with a Veſſel full of the medicinal Liquor by means of a ſmall leathern Pipe: This Liquor might flow into the *Abdomen*, as faſt as the dropſical *Lympha* paſſed off through the other *Trochar*; whereby the dropſical *Lympha* might be conveyed off, to what Degree it ſhall be thought proper; and that without any Danger of a *Syncope* from Inanition; becauſe the *Abdomen* would, through the whole Operation, continue diſtended with Liquor, in ſuch a Degree as ſhall be found proper, by raiſing or lowering the Veſſel with the medicinal Liquor in it.

It is probable, that, if the Surface of the medicinal Liquor be about a Foot higher than the *Abdomen*, it may be ſufficient for the Purpoſe.

It were eaſy to find the Force with which the *Abdomen* is diſtended by the dropſical *Lympha*, by ſeeing to what Height it aroſe in a Glaſs Tube fixed to the *Trochar*; which Tube being taken away, it might, I ſuppoſe, be ſufficient to have the medicinal Liquor flow in from a leſſer perpendicular Height, than that to which the dropſical *Lympha* aroſe in the Glaſs Tube. I am,

S I R,

Your humble Servant,

Stephen Hales.

Fig. 6.3 The letter of the Reverend Stephen Hales to the Royal Society in 1724 [13], suggesting peritoneal lavage through two abdominal catheters. At that time contributions to the published *Proceedings of the Royal Society* (one of the oldest scientific bodies in the world, founded in 1660 by Sir Christopher Wren amongst others) were normally in the form of letters to the secretary, and his was a comment on the paper he had heard Charles Warrick present (see text).

the idea of double catheters through which fluid could be perfused. Warrick instilled 'cohore wine and Bristol water' after withdrawl of the ascitic fluid, and found that with a ratio of two parts wine to one of water, the ascites did not recur; but the patient fainted during the removal of the ascitic fluid. Hales suggested that, at the same time

as the fluid was withdrawn from one trocar inserted into the abdominal cavity, fluid could be infused by means of a second trocar introduced into the opposite side of the abdomen—all without local or general anaesthetic, of course—with the very reasonable intention of avoiding the syncope.

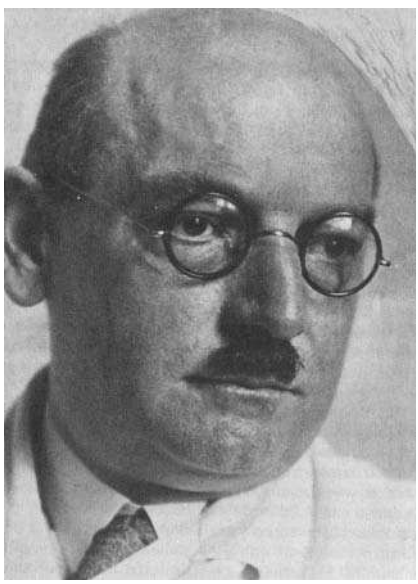
Major interests from the middle of the nineteenth century were absorption in general, and the peritoneal cavity in relation to the fast-developing field of abdominal surgery. In 1862 Friedrich von Recklingshausen (1833–1910) made a detailed and remarkably accurate description of its anatomy, histology and physiology [15] noting even the lymphatic drainage to which attention would be directed more than a century later. Georg Wegner [16] working in the University Surgical Clinic in Berlin is usually credited with the first modern studies of peritoneal infusion in 1877 [17]. Although the main object of his studies was not exchange but deaths during abdominal surgery, in experiments on rabbits he established both that infusion of cold fluids into the peritoneum reduced their temperature, and that solutions of salts were absorbed and hypertonic solutions of sugar, salt or glycerine increased in volume when infused into the cavity. Even more directly relevant were studies shortly afterwards by the famous English physiologist Ernest Henry Starling (1866–1927) (Fig. 6.4a), who contributed so notably to studies of fluid exchange in capillaries, and of cardiac function. Starling and his colleagues Alfred Tubby and J.B. Leathes [18,19], then working at Guy's Hospital in London, set out to study in detail the exchange into and out from the peritoneal and pleural cavities in the light of Graham's and later work on diffusion. They established also that fluid entered or left the peritoneum according to the concentration of saline in the perfusing fluid: fluids more concentrated than blood plasma withdrew fluid, whist isotonic fluids remained at a constant volume for many hours, neither being absorbed nor withdrawing fluid. Transport of water and solute was bidirectional. These observations are crucial to the performance of peritoneal dialysis. They showed also that dyes of higher molecular weight such as indigocarmine or methylene blue could pass across the peritoneum in either direction. If anyone is to be designated as the 'father' of peritoneal dialysis, it surely should be Starling.

At almost the same time and independently, W.N. Orlow [20] a pupil of Heidenhain working in St Petersburg in Russia, made similar detailed observations in dogs. However, in contrast to the purely mechanistic theories of diffusion favoured by Starling and others such as Hamburger, Orlow concluded that once diffusive and osmotic considerations had been satisfied, absorption from the peritoneal cavity was an active process ('*es aktiven Anteil nimmt*'), following his mentor's long-held ideas on the subject of secretion, an idea which recurred in several writings during the next 20 years.

Further studies refined the variables influencing this exchange. Work in Germany by Rudolf Klapp of Greifswald, in 1902 [21], showed that cooling and heating the fluid lessened or enchanced exchange. He concluded correctly that most of the reabsorption of water-soluble substances from the peritoneum must take place into the blood vessels lining the peritoneum, and not through the membrane itself as had been supposed. Clairmont and Haberer in 1905 showed also that increasing or decreasing bowel movements using drugs enhanced and lowered absorption,

(a)

(b)



(c)

(d)

Fig. 6.4 Some pioneers in peritoneal dialysis. (a) Ernest Henry Starling (1866–1927) provided the physiological basis for understanding fluid exchange through the peritoneum in the 1890s (courtesy University Colleger, London). (b) Tracy Putnam (1894–1975) developed these ideas in the early 1920s, and introduced the idea of the peritoneum as a membrane for dialysis (courtesy Alan Mason Chesney Archives, Johns Hopkins University). (c) Georg Ganter (1885–1940) performed the first tentative exchanges in humans in 1923 (courtesy Münchener Mediziniche Wochenschrift). (d) John B Wear of Wisconsin performed the first peritoneal dialysis in the United States in 1936 and first had a patient survive after peritoneal dialysis in 1938 (from McBride PT, *locät*.) [43].

respectively. Later in 1916, Max Rosenberg [22] of Charlottenburg in Berlin, repeated and expanded Owen Rees' observations of 70 years before [23], that urea was present in equal quantities in peritoneal and pleural fluid, as in plasma in uraemic patients with nephritis—a crucial observation without which the idea of removing urea by this route would not have arisen.

In the United States, in 1920, the anatomist R.S. Cunningham [24] of the Johns Hopkins Hospital studied in detail intraperitoneal infusion of 10% dextrose in rats, noting that absorption was slow, taking many hours. He made also what must be the first observations of damage to the mesothelial layer (a term he employed) from its exposure to laked blood and to particulate matter such as starch, but (most importantly from our point of view) also from exposure to hypertonic glucose, which produced similar patterns of injury:

> a few cells had become almost separated from the underlying structure and were attached by only a small pedicle. Areas scattered over the diaphragm … were bare; the cells having desquamated … many of the cells were rounded up and undergoing division. The cytoplasm of the cells became more basophilic as they rounded up and increased in size.

He noted also that 'under very high magnification' these large mesothelial cells 'invariably presented a surface which was covered with fine projections … they varied considerably in length and width, and were somewhat irregular'—thus forseeing what has been confirmed by electron microscopy only in the 1980s.

A.J. Clark [25] of Guy's Hospital, London and Cape Town also studied absorption of isotonic fluids of varying compositions, again noting that diffusion was slower or faster according to temperature, and to vasoconstriction or vasodilatation. He also studied, using freezing point depression, the attraction of water into the peritoneal cavity by hypertonic dextrose solutions.

All this early work had been done with purely physiological goals in mind, but the first clinical application of fluid exchange within the peritoneum came during the First World War, when the noted American paediatrician Kenneth Blackfan (1883–1941) and his colleague Kenneth Maxcey at the Johns Hopkins Hospital used the peritoneal membrane to administer salt and water to dehydrated children [26]; this was studied further by Dan Darrow and his colleagues in subsequent years [27]. Blackfan and Maxcey make the interesting comment that this treatment was 'routine' in the department run by Sir Archibald Garrod (1857–1936) at St Bartholomew's Hospital in London, from whom they derived the idea.

The accumulation of all these data could now lead to a consideration of the peritoneal membrane as a diffusing surface capable of removing substances from the body. The worker who undertook this task was the American neurologist Tracy Jackson Putnam (1894–1975) (Fig. 6.4b). He worked, yet again, at the Johns Hopkins Hospital, the alma mater of Abel, and must surely have discussed the latter's work in vividiffusion with him, and Blackfan's studies with him (although surprisingly he quotes neither paper). Putnam published a detailed study in 1923 [28], reviewing extensive work on the peritoneum 'as a dialysing membrane'. He examined dwell time, flow rate, ultrafiltration and solute concentration in peritoneal dialysis in cats, rabbits and a few dogs, noting a number of features still important in peritoneal dialysis

1478 MÜNCHENER MEDIZINISCHE WOCHENSCHRIFT.

Aus der Medizinischen Klinik Würzburg.
(Vorstand: Prof. Morawitz.)

Ueber die Beseitigung giftiger Stoffe aus dem Blute durch Dialyse.

Von Prof. G. Ganter.

Wir wissen, dass die Urämie durch Stoffe zustande kommt, die infolge ungenügender Tätigkeit der erkrankten Nieren im Körper retiniert werden.

Die Natur dieser Urämiestoffe ist unbekannt, nur soviel steht fest, dass bei vorhandener Urämiebereitschaft der Rest-N-Gehalt des Blutes erhöht ist. Da eine Abhängigkeit besteht zwischen der Urämiebereitschaft und dem Reststickstoffgehalt des Blutes, so sind wir gewohnt, diesem Reststickstoffgehalt des Blutes eine besondere Beachtung zu schenken.

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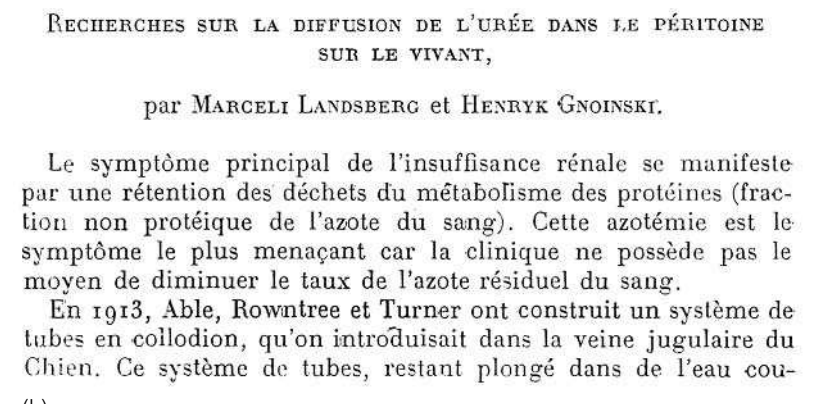


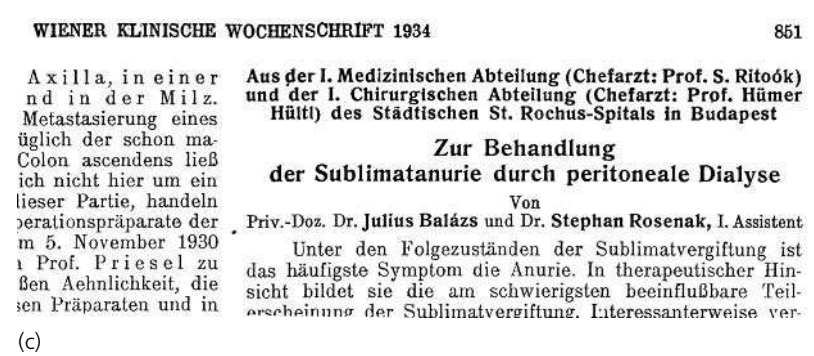
RECHERCHES SUR LA DIFFUSION DE L'URÉE DANS LE PÉRITOINE SUR LE VIVANT,

par MARCELI LANDSBERG et HENRYK GNOINSKI.

Le symptôme principal de l'insuffisance rénale se manifeste par une rétention des déchets du métabolisme des protéines (fraction non protéique de l'azote du sang). Cette azotémie est le symptôme le plus menaçant car la clinique ne possède pas le moyen de diminuer le taux de l'azote résiduel du sang.

En 1913, Able, Rowntree et Turner ont construit un système de tubes en collodion, qu'on introduisait dans la veine jugulaire du Chien. Ce système de tubes, restant plongé dans de l'eau cou-

(b)



WIENER KLINISCHE WOCHENSCHRIFT 1934 851

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Aus der I. Medizinischen Abteilung (Chefarzt: Prof. S. Ritoók) und der I. Chirurgischen Abteilung (Chefarzt: Prof. Hümer Hültl) des Städtischen St. Rochus-Spitals in Budapest

Zur Behandlung der Sublimatanurie durch peritoneale Dialyse

Von
Priv.-Doz. Dr. **Julius Balázs** und Dr. **Stephan Rosenak**, I. Assistent

Unter den Folgezuständen der Sublimatvergiftung ist das häufigste Symptom die Anurie. In therapeutischer Hinsicht bildet sie die am schwierigsten beeinflußbare Teilerscheinung der Sublimatvergiftung. Interessanterweise ver-

(c)

Fig. 6.5 Three key early papers on peritoneal dialysis: (a) Ganter (1923) [29], (b) Landsberg and Gnoinski (1925) [32] and (c) Balázs and Rosenak (1934) [35]. Ganter was the first to suggest peritoneal dialysis for the treatment of uraemia, and do single exchanges in two patients. He was unaware of Putnam's work [28] of the same year. Landsberg and Gnoinski independently did animal experiments to treat uraemia, not knowing of Ganter's work. The first serious attempt to treat acute uraemia in humans was that of Balázs and Rosenak in Budapest in 1934, in three patients with mercuric chloride poisoning.

today, including the relation between molecular size and rate of removal, and noted that 'changes in volume represent osmotic forces at work'. Putnam did no more work in this field, but became later a noted neurologist at Harvard, and contributed much original work in this field.

Meanwhile Georg Ganter (1884–1940) (Figs 6.4c and 6.5) had begun work at about the same time as Putnam in the medical clinic in Würtzburg in southern Germany, as resident in the department of Professor Morawitz. He was probably aware of the German physiological work on peritoneal exchange mentioned above, but Putnam's paper appeared too late for him to have read it, and he did not quote it. The main immediate stimulus to Ganter seems to have been Necheles' work using peritoneum *ex vivo* in an apparatus, in that he pointed out in his paper that it would be simpler to use the peritoneum *in situ* within the body. From his own account [29], however, he had already tried a single 750 ml pleural lavage in a uraemic young man with glomerulonephritis as early as 1918, with the stated intention of removing the uraemic poisons. If so, this was an imaginative leap, and one wonders if the idea had been stimulated by Rosenberg's paper [22] of 2 years previously on urea in peritoneal fluid in uraemic patients with ascites, mentioned above.

Necheles in turn was aware of Ganter's work, and in a letter to Abel [30] he mentions his criticisms of it, and also makes an interesting note that he had tried to replicate Ganter's work, but without success. Ganter also knew of Blackfan's work using the peritoneum in children (although he does not quote it directly, stating merely that '*in der Kinderheilkunde … amerikanischer Aertze etc.*') and mentions that several German paediatricians had followed Blackfan's example in 1921–1922, whose papers he does cite—Bakes, Renz, Mayer and Weverinck—suggesting that the practice of intraperitoneal infusion of fluids was widespread in Germany.

Ganter's short paper [29] is a brief account first of his 1918 experiment just described, and then experiments carried out in 1922 in rabbits and guinea-pigs whose ureters were tied to render them uraemic. This was the first attempt to remove uraemic toxins by peritoneal dialysis, if we ignore Putnam's unpublished experiments which he mentions only briefly [28]. These animals were dialysed on four occasions, using 40–60 ml of isotonic saline solution every 3 hours; there was no dwell time of the fluid within the abdomen. Sometimes the fluid was difficult to recover, but he thought the animals' condition was 'improved'.

Ganter continued with brief descriptions of a single infusion and removal of 1.5 L of isotonic saline into the peritoneum of an unfortunate woman who had just become uraemic from occlusion of both her ureters by spreading carcinoma of the uterus[1], and similarly of 3 L into a diabetic patient with ketoacidosis. These single

[1] McBride in his book [p. 81] writes of a patient 'who had suffered renal failure following childbirth. In a series of exchanges Ganter instilled from 1 to 3 liters of solution and let it dwell from 30 minutes to 3 hours each time … the patient subsequently died, and Ganter noted that he had not been aware that he would have to continue the therapy in order to keep the patient alive'. McBride must be confusing this account from another paper, as no such patient or comments appear in Ganter's paper of 1923, and he published no other. He also says that Ganter recommended dextrose, but Ganter mentions only 'hypertonische Soluzionen'.

exchanges represent the beginnings of therapeutic peritoneal dialysis. Both were judged by Ganter to have been 'improved' by the manoeuvre, although this now seems unlikely. Despite the paucity of his clinical data, he finishes his paper by making several important recommendations: that the fluid must be sterile, local anaesthetic for insertion of the needle is kind, and that access and removal of fluid could be difficult but hypertonic solutions can be used to limit fluid retention.

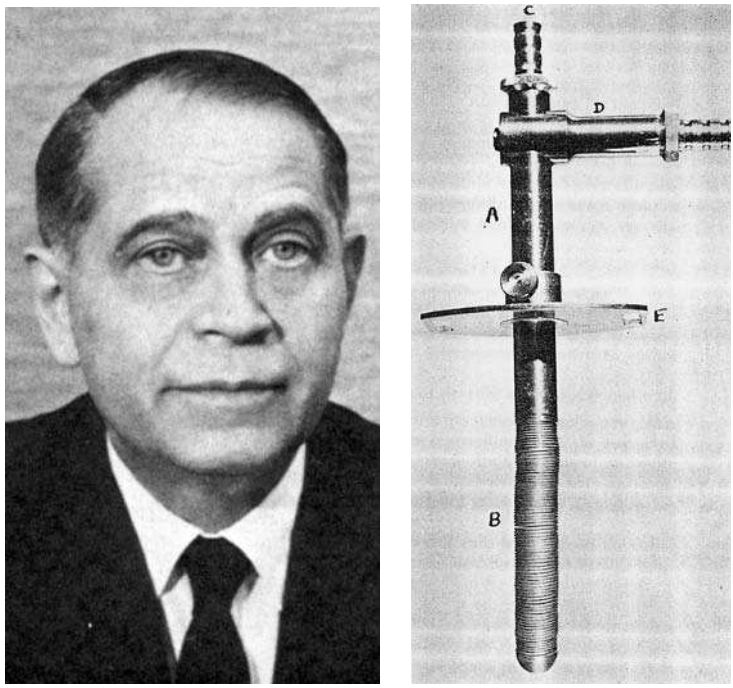
Ganter then moved to Rostock as chief of medicine, but made no further studies in the area of dialysis. There in 1937, as Horst Klinkmann (a successor in Rostock) records [31], although not a Jew himself he was dismissed by the Nazis and was forbidden work for refusing not to treat Jewish patients: 'I will treat every Jew as well as every other human being' he wrote in reply. Klinkmann says Ganter committed suicide in 1940, to avoid being sent to a concentration camp—a fate which we have seen already befell Hermann Strauss in 1944.

A few others, however, were stimulated to take peritoneal dialysis further. A factor in this interest may have been that awareness of acute, potentially reversible renal failure was probably greater in German-speaking countries during the 1920s than anywhere else because of early descriptions in the First World War, as we shall see in Chapter 11. The first of these were a forgotten pair of workers in Poland, Marceli Landsberg and Henryk Gnoinski, who published their short paper in French in 1925 (Fig. 6.5) [32]. They note at the end of their paper 'apres avoir fini nos recherches, nous avons appris que Ganter (de Würtzburg) a obtenu presque les mêmes résultat … [en] cobayes urémiques', so they should have even greater credit for their studies. They reasoned that because of the difficulties with anticoagulation of blood experienced by Abel and his colleagues, it was better to use the peritoneum 'comme dialyseur naturel d'une grande perméabilité'. They dialysed normal rabbits and animals made uraemic using uranyl nitrate, employing a metal trocar to instil, and a puncture of the lower abdomen to release, the Ringer's solution used. Significant quantities of urea could be removed with a reduction in blood urea.

The next year a young Hungarian called Stephen Rosenak (b. 1900) (Fig. 6.6) [33], together with P. Siwon, published studies of peritoneal exchange in dogs made uraemic by nephrectomy [34] done during 1925 and 1926 in the university surgical clinic in Bonn. Their study is much more extensive and detailed than the brief reports of Ganter and Landsberg and Gnoinski, and is a landmark paper in the history of peritoneal dialysis. They had made for themselves a special cannula for introducing and draining the fluid; thus the unknown Herr Geissler was responsible for the first ever peritoneal dialysis catheter:

> the choice of cannula gave us difficulties to begin with. A simple glass tube was blocked by intestinal loops etc. during the course of the study. We were lucky to get from Geissler in Bonn a home-made cannula, as thick as a pencil, which at its end had a butt with multiple holes like a watering-can, which served us very well. This device, with the aid of another technical point, i.e. the suturing of the omentum [to the abdominal wall] were the reasons why inflow and outflow of fluid were regular.

They found a marked reduction in blood urea using a 5% glucose solution for peritoneal dialysis, but it was not until 1934 in Budapest that Rosenak tried dialysis in two



(a) (b)

Fig. 6.6 (a) Stephen Rosenak (1900–198?) a Hungarian urologist who emigrated from Berlin to Britain and then the United States who worked on both peritoneal dialysis before and after, and haemodialysis after the Second World war. (b) The double peritoneal catheter he and Oppenheimer designed later in 1948 (see Chapter 10, ref. [20]). This was probably the first device specifically for instilling peritoneal dialysis fluids in man, since all other attempts up to that time—and for some years beyond—used various catheters available but designed for other purposes. (Courtesy Dr Rosenak, from [33].)

young women with acute renal failure from mercurial poisoning—a good choice, since recovery was known to occur, provided that the patient did not die of the uraemia first. Rosenak and his senior colleague Julius Balázs (Fig. 6.5) used isotonic saline and, this time, hypertonic dextrose (42 g/L) as the dialysing fluid in this first serious attempt to use peritoneal dialysis clinically, but both patients died after 7 and 5 days despite single dialyses in each of 12 and 19 L, which both dropped the blood urea substantially and also removed some mercury [35]. This was the first (and for several years the only) clinical use of dextrose to extract fluid from the peritoneum, so that patients did not become overloaded with fluid during dialysis. Rosenak's involvement with the treatment of uraemia was to last more than a quarter of a century in two continents—having fled from Germany in 1938 to work at the Hammersmith Hospital in London, he went on to the Mt Sinai Hospital in New York in 1941, where he described and made one of the first purpose-made peritoneal dialysis catheters (see Chapter 9), as well as building a flat-plate haemodialyser in 1951 and other

machines of his own design (see Chapter 12).

Important laboratory studies at this time was performed also by Desider Engel of Prague [36], who showed in two papers from 1927 that proteins could penetrate into the peritoneal cavity—and be lost into the peritoneal fluid. He demonstrated also that the entry of dyestuffs into the peritoneal fluid depended additionally upon on acidity (pH) and the molecular size of the substance diffusing and protein binding. Also in 1927, H. Heusser and H. Werder in the surgical clinic of the University of Basel in Switzerland described their experiments in dogs [37], deciding that peritoneal dialysis could have clinical application, and defining how best it might be done:

> In humans we have had the opportunity three times to perform dialysis. Clinical success however eluded us—because at that time the dialysis flow rate was too low. However it turned out that clearly the dialysis procedure can be carried out in humans as well.

It is a pity they give no more details, because this was the first attempt in humans following Ganter's single exchange in one patient, in 1923, preceding that of Rosenak by 7 years. Thus the first proper, detailed account of peritoneal dialysis in humans,

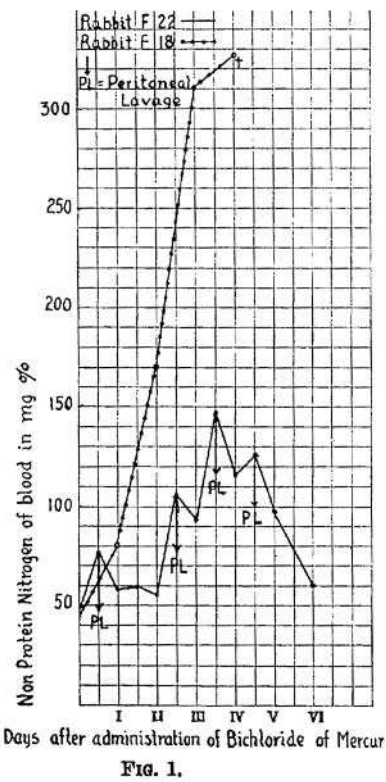


Fig. 6.7 A figure from von Haam and Fine's 1932 paper [39] in which they showed not only that uraemia could be controlled, but that animals could survive experimental acute renal failure using this technique, leading directly to Rosenak's paper of 1934.

with biochemical if not clinical success, remains that of Stephen Rosenak and Julius Balázs in 1934.

Sidney Bliss and colleagues in 1931 studied nephrectomized dogs [38], which they managed to keep alive from 13 to 16 days using their peritoneal dialysis. In 1932, E. von Haam and A. Fine of Louisiana State University did an impressive clinical trial on reversible acute renal failure in rabbits made uraemic by an administration of mercuric chloride [39]. Eight of nine control rabbits died within 3–4 days, but four of six rabbits treated with two to four intermittent peritoneal dialyses recovered (Fig. 6.7). Dialysis was abandoned in one animal which died after 6 days. Thus they demonstrated clearly that reversible acute uraemia from mercurial poisoning could be managed by dialysis, and although Rosenak and Balázs do not quote their experiments (or those of Bliss) they may have been unaware of these papers published in English in America. Further animal studies were done also by Von Jeney in Hungary [40] in 1932 using a mercuric chloride model in dogs.

Clinical peritoneal dialysis occurred also in the United States during the 1930s, in addition to these dog studies. At the Wisconsin general hospital, urologist John B. Wear (Fig. 6.4d) and his colleagues Eli Sisk and A.J. Trinkle reported multiple

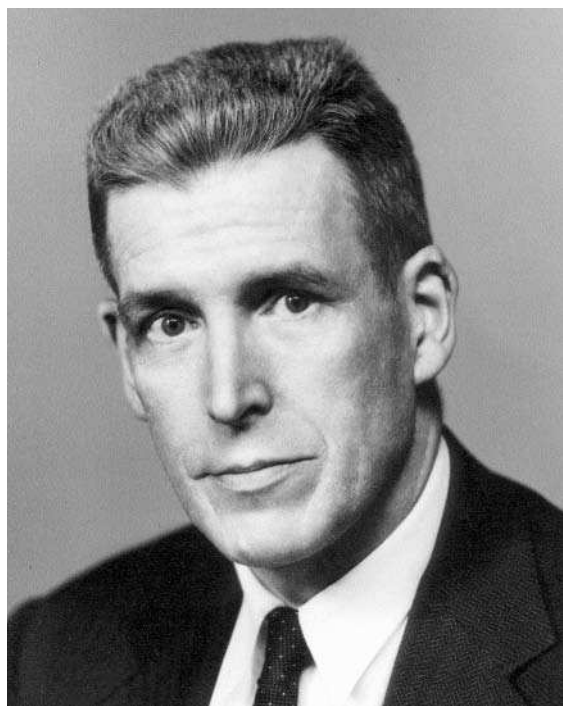


Fig. 6.8 Jonathon R. Rhoads of Philadelphia (1907–2002) who not only performed peritoneal dialysis in 1938 but also constructed and used an artificial kidney based on cellophane tubing in 1944 (see Chapter 11 for details). (Courtesy collection of the University of Pennsylvania Archives.)

dialyses in five patients suffering from renal failure from 1936 onwards [41]. Of these, one patient with renal and bladder stones supposedly suffering from 'reflex anuria' and obstruction, was maintained by intermittent peritoneal dialysis, using for the first time a solution similar to the composition of the plasma (Hartmann's solution) and a gallbladder trocar for abdominal access. This treatment was continued until an operation to relieve the obstruction could be done, with recovery of renal function. At last some tiny success emerged after 15 years of effort. Dialysis may have contributed to the survival of this patient, which preceded the first patient survival from haemodialysis by 7 years, although equally one could argue that this patient was going to recover anyway. Jonathon Rhoads (1907–2002) (Fig. 6.8), a surgeon in Philadelphia, also used intermittent repeated dialysis for the first time in clinical studies in 1938 [42], but both of his patients, who turned out to be suffering from chronic irreversible renal failure, died. Only 6 years later, he tried haemodialysis (see Chapter 11).

With hindsight, potentially much more could have been achieved much earlier, and it is not clear just why peritoneal dialysis made such little headway as a treatment for acute reversible renal failure during the 1920s, and especially the 1930s, when it was clear it could be of use to tide patients over a period of reversible oligoanuria . Although what would now be called acute—and potentially reversible—renal failure in the form of mercurial poisoning had been targeted clearly by several groups of clinicians, cases of any form of acute renal failure remained rare until the 1940s, as discussed in Chapter 12 below. Really long-term peritoneal dialysis for irreversible disease was out of the question, especially as dialysis was performed continuously by almost all investigators. In addition, access to the peritoneal cavity was a continuing problem and infection a constant hazard, but the defining obstacle was probably the lack of any idea of how much dialysis had to be performed and for how long in order to maintain well being, and how best to undertake the procedure—above all what fluid would best be used for dialysis. Knowledge of the chemical anatomy and even the existence of the various functional compartments of the body described by Gamble and then Darrow was slow to spread to most clinicians. The composition of fluids used in early attempts at dialysis is discussed in Chapter 10 and summarized in Table 10.1. Finally, and probably the most important factor, only a handful of investigators turned their attention to the problem. It remained for the 1940s to establish, rather suddenly, that peritoneal dialysis was a viable treatment for acute uraemia.

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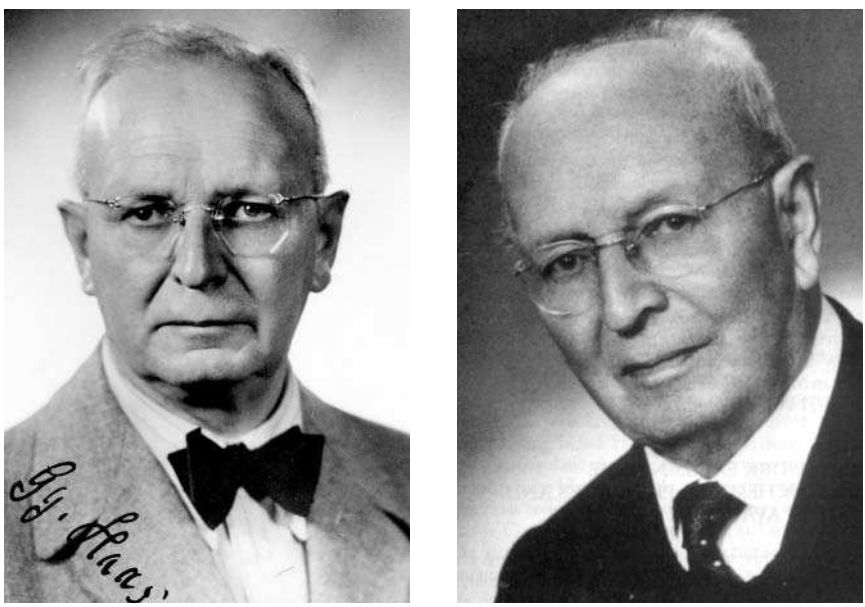
Chapter 7

The first haemodialyses in humans: the introduction of heparin and cellophane

The work of Georg Haas

In parallel with the work on peritoneal dialysis just outlined, much happened in the field of haemodialysis during the 1920s and 1930s, although, as with peritoneal dialysis, the clinical outcomes were minimal. In his 1923 paper, Ganter quotes, besides the work of Necheles as outlined above, the first paper of Georg Haas (1886–1971) (Fig. 7.1), which again had just appeared in 1923. Haas' major but eventually unsuccessful contribution to the development of dialysis was first highlighted by Drukker [1], and has been discussed since, for example by Benedum, Wizemann and



(a) (b)

Fig. 7.1 (a) Georg Haas (1886–1971) as a younger man and (b) in 1968, aged 82. Haas lived on to see the successful application of the techniques he pioneered during the 1920s to the treatment of first acute and then chronic renal failure. ((a) courtesy Dr H-G, Sieberth; (b) courtesy Dr Jost Benedum, from [1] with permission).

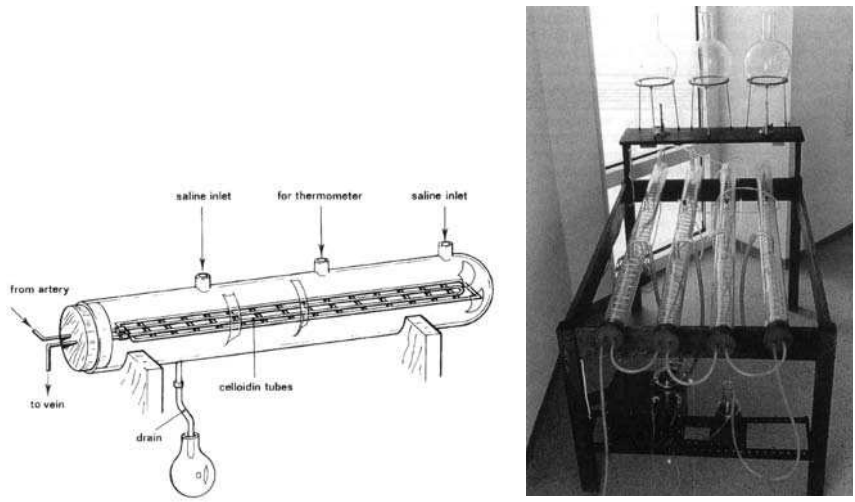
Ritz [2–5]. Haas was born in Nürnberg, the fifth son of a wealthy factory owner. He studied in Freiburg under Aschoff, qualifying in 1909, and then moved to study with Franz Hofmeister in Strassburg, following him to Kiel. He first encountered dialysis through its use for separating of amino acids in Hofmeister's laboratory in Strassburg in 1911. Then, his dialysis membranes were the inner layer of the reed stalks, which when dried gave convenient tubes, and had been in use for this purpose since 1902 [6]. These he employed to separate metabolites from dog blood. When the First World War began in 1914, Haas had just moved to Giessen and was drafted back into clinical work; he met renal failure in the form of so-called 'trench' nephritis, some with fatal uraemia. Like Necheles, he was to describe later his helplessness in the face of uraemia, an experience common to all the pioneers of dialysis. Unaware of the experiments in Baltimore, Haas considered applying his laboratory knowledge to the problem [7]:

> given the hypothesis that uraemia is caused by retention of products which should be excreted in the urine and presumably could be removed by dialysis, I thought again of my dialysis experiments in my previous metabolic studies.

Clearly both Haas and Necheles, unlike Abel (at least to start with), both had a clear concept of using dialysis to remove uraemic 'toxins' from the beginning of their work. Haas tried various membranes, still a major stumbling block: reed, paper and peritoneum, but none were satisfactory. In the meantime he submitted successfully his *Habilitationsschrift* on indican concentrations in the blood as an indication of renal failure. However, his experiments were halted in 1917 when he was drafted to Romania because of a typhus epidemic there. When he returned to Giessen in a now ruined Germany in 1919 he had clinical responsibilities, and it was not until Necheles' paper of 1923 rekindled his interest in dialysis that he began work again, even though he was critical of Necheles' work [7,8], believing that his (commercially available) hirudin was more toxic than Necheles claimed [9]. Still unaware of the Baltimore work according to his own account, he heard of collodion through its use in the chemistry laboratory of the Austrian 1923 Nobel Prize winner, Fritz Pregl of Vienna, who had previously collaborated with Abel, analysing some of the latter's dialysates. In 1924 Haas was appointed director of the outpatient clinic in Giessen, where his studies on human dialysis were performed. He remained in Giessen for the remainder of his life, but from 1930 onwards devoted himself principally to issues of public health medicine.

Haas' first task was to make suitable colloidon membranes, as Abel and his colleagues had to, and this he achieved making tubes up to 120 cm long from this delicate material, and constructing dialysers with several such tubes and a surface area of between 1.5 and 2.1 m^2 (Fig. 7.2). He still had to use hirudin as the anticoagulant, and it took some time to locate a reasonably non-toxic product. Haas was then able to perform dialysis in dogs, and demonstrated the removal of indican and potassium iodide—two substances, as he had himself shown, that accumulated during kidney failure.

Now he was ready to dialyse a human patient with uraemia because, as he wrote in his paper of 1925 [10]: 'this is a condition against which the doctor stands otherwise



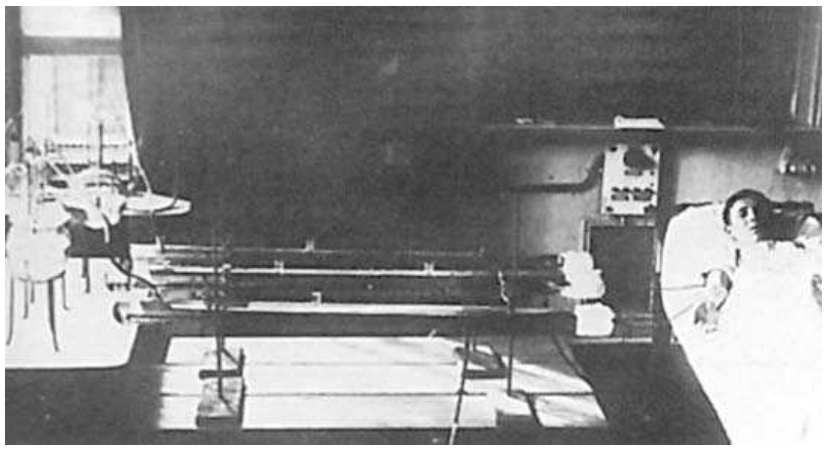
(a) (b)

Fig. 7.2 Haas' dialyser. (a) A diagram of one component showing the design to be very similar to that of Abel and his colleagues, although he was unaware of their work to begin with. The diagram has been relabelled in English. Several of these units could be put together to make an artificial kidney. (b) A reconstruction of Haas' kidney in the renal unit in his home town, Giessen in Germany. (From [5] with permission.)

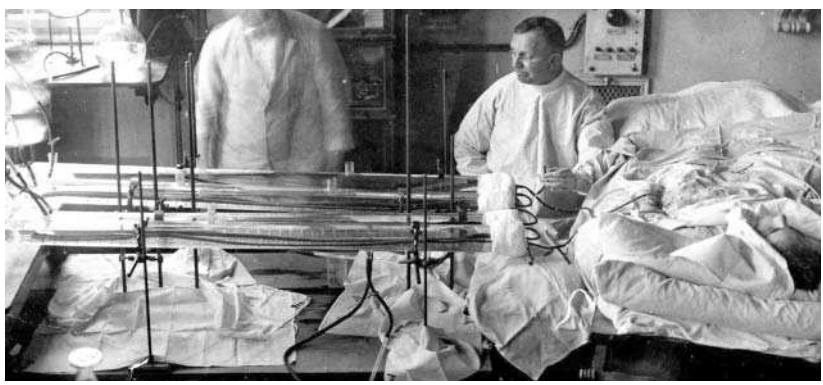
powerless'. In these experiments he was assisted by the surgeon Dr von der Hulten. This first tentative trial dialysis, lasting only 15 minutes, was performed in October 1924 and no details are available, but on 18 February 1925 he dialysed a young boy dying of uraemia for 35 minutes using a venovenous circuit (Fig. 7.3). The next year, four more patients were dialysed for 30–60 minutes. Haas' early dialysis procedures involved withdrawing venous blood, dialysing it against Ringer's physiological solution, and then returning it through the same channel into the circulation [11]. This fractionated dialysis, and the brevity of these early attempts (imposed by the toxicity of the hirudin), meant that the effect on the patient was negligible. In addition, Haas had the important insight of solute exchange from cells into the blood:

> During continuous dialysis, the blood urea nitrogen concentration diminishes first only slightly, because the stores of nitrogenous substances in the tissue restore the concentration in the blood … thus blood serves as a transit compartment for substances to be dialysed.

It was 2 years before Haas attempted dialysis again, probably stimulated to do so because a new anticoagulant had become available: *heparin*. This, despite increasing competition, remains the standard anticoagulant for haemodialysis 70 years later [12]. Heparin has played such a major role in both the introduction and the success of haemodialysis that dialysis almost becomes unthinkable without it.



(a)



(b)

Fig. 7.3 (a) The second dialysis in a human being by Haas, on a young uraemic boy on 18 February 1925. (b) Haas performing a dialysis on a young girl (seen on the right) in 1926. The details of the dialysis apparatus are clearly seen. Note that the procedure is being performed in a lecture theatre and not a hospital ward. (From [1,3] and Dr Willi Haas, nephew of Georg Haas, via Dr Jost Benedum.)

Heparin and its controversial discovery: the disputed role of Jay Maclean

The discovery of heparin has been the source of some controversy [13–19]. An anti-coagulant phospholipid was described first in an extract of liver in 1916 [13] by a young medical student, Jay Maclean (1890–1957) (Fig. 7.4a, b) [14–17]. Maclean was born in San Francisco, the son of a surgeon who died when he was only 4 years of age. He supported himself as a labourer before entering pre-medical studies at the University of California in 1914. He came to the Johns Hopkins Hospital in 1915, and was working as a second-year medical student in the same building which housed

(a)

(b)

(c)

Fig. 7.4 The discoverers of heparin. Jay MacLean (1880–1957) as a young man (a) and later in life (b), whose student work showed that liver contained an anticoagulant principle. (c) William Henry Howell (1860–1945) as a young man, who supervised Maclean's work and later prepared and named 'heparin', which was one of the two vital components which made clinical dialysis a practical reality. (From [18].)

Abel's laboratory. Maclean's chief, the noted haematologist and physiologist William H. Howell (Fig. 7.4c), suggested he study a number of thromboplastic (clot-promoting) substances. Maclean did this, as well as studying one prepared from liver:

> The hepatophosphatid on the other hand when purified by many precipitations from alcohol at 60° had no thromboplastic effect, and in fact shows a marked power to inhibit acoagulation. The anticoagulating action of this phosphatid is being studied and will be reported upon later.

Howell initially did not welcome the discovery, because it disagreed with his theories of blood coagulation [15–18]; Maclean later recalled that he was an outsider in the laboratory [14], but both he and Howell [17] eventually referred to each other as their 'best friend'. Maclean left for Philadelphia in 1917, but stated later that he hoped there to continue work on the phospholipid he had discovered. In fact he did work there on cephalin, but on its procoagulant activity rather than on it as an anticoagulant [20]. After a period with the American army in France, he took his MD in 1919, and returned to the Hopkins, but in the surgical service under Halsted.

Meanwhile in 1918 [21] and 1923 [22] Howell published papers with a retired paediatrician who came to work in his laboratory, Luther Emmett Holt (1855–1924) [23], in which credit was given to Maclean, and in which the enduring name of *heparin* was used for the new principle, because of its origin in the liver (Latin *hepar* = liver). Howell and Holt became renowned for their discovery, whilst Maclean's contribution languished. In the following years Maclean had an unsatisfactory and obscure career, first as an instructor in clinical surgery (for which he appears to have had no talent, and practiced little or not at all) in California; he then spent some time in Europe, returned to New York in 1924, and then worked in pathology with Ewing at Cornell from 1927 to 1939. During this time he used heparin to anticoagulate dogs given pneumonia and abdominal adhesions. He then went to a post in experimental surgery at Ohio State University in Columbus, undertaking private practice also using mainly radiotherapy. At this time he published further papers on heparin, using commercial heparin clinically but also working on its purification in the laboratory [24–26]. For years he planned a monograph on heparin which was, however, never completed. Finally, Maclean worked in administrative posts in Washington and Savannah, Georgia until his death in 1957. His role in the discovery of heparin was only noted publicly in 1945, and then after his death in 1957.

Howell's role in the discovery of heparin

William Henry Howell (1860–1945) was, like Abel, a pupil of physiologist Newell Martin at the Hopkins (Fig. 7.4c) [18]. He graduated in 1884 with a doctoral thesis on blood coagulation, which remained a central interest for the remainder of his career; only 8 years later he was appointed professor of physiology. Howell postulated that the body must produce, as well as substances promoting coagulation (thromboplastins), one or more natural anticoagulants. It was with this in mind that Howell set his student Maclean to work, with the (to him) surprising result that some phosphatids from the liver were not procoagulant, but *anti*coagulant. Maclean wrote much later that Howell permitted him only to include these unexpected results in the text of the paper, and not in its title, summary or conclusions. Significantly, also, Howell did not appear as co-author, although in his paper of 1917 and 1918 Howell did give Maclean credit [21]. In a letter to Charles Best (see below) in 1940, Maclean wrote that Howell invited him to be a co-author of the 1918 paper, but he (Maclean) declined because 'I had participated to such a small extent in this later work and I did not feel entitled to the privilege offered'.

In 1918 Howell was still under the impression that the principle was a phosphatid—i.e. a phospholipid. During the next 10 years he worked determinedly

and almost alone at the purification from dog liver of what he continued, confusingly, to call simply 'heparin', eventually using aqueous rather than ether extraction, clearly indicating that it could not be a lipid. That this was so was confirmed in 1925, when he demonstrated the absence of phosphorus in the molecule. By 1928 he had identified it as a sulphur-containing sugar compound, a glycosaminoglycan [17,28], and most readily obtained from intestine rather than liver—its usual source today. The name 'heparin' however, now quite illogical, was still employed and has proved durable.

It appears in retrospect in the light of both Maclean's letters to Best [18] and his posthumous autobiographical account [15], that Howell was always willing to give Maclean full credit both publicly and privately for his 'description' or 'discovery' of heparin; but that Maclean became progressively disillusioned by the fact that in the public arena only Howell received credit. This led to a sad campaign from 1940 onwards to establish his 'priority', which became almost an obsession. Only 6 years after his death, in 1963, a plaque to Maclean was put in place at the Johns Hopkins: 'In recognition of his major contribution to the discovery of heparin in 1916 as a second-year medical student in collaboration with Professor William H. Howell'.

The first use of heparin for haemodialysis

As early as 1923, a crude low-potency heparin was available commercially for experimental use. Far away in China, in the physiology department of the Peking Union Medical College, where Necheles had emigrated, news of this new anticoagulant arrived, probably through Clarence Mills, a coagulation expert also working in Peking (now Beijing) [27]. Necheles used it to perform more dialyses on dogs with his Chinese collaborator R.K.S. Lim, but mainly to extract substances of physiological interest [29–31]—a return to Abel's original use of the technique. Necheles continued to be interested in dialysis, and wrote a review in an Israeli journal as late as 1952! [32]. Meanwhile the ubiquitous Rowntree, now Chief of Medicine at the Mayo Clinic, used his knowledge of vividiffusion to study the effect of heparin in an extracorporeal circuit in dogs, using a single collodion dialysing tube [33–35]. Rowntree and colleague Takuji Shionoya rediscovered the important effect of turbulence of blood in avoiding pooling and thrombosis that von Hess and McGuigan had noted a decade earlier, but studied this phenomenon in much greater detail.

Also using the new anticoagulant, in 1928 Haas started again and dialysed two patients on a 1.5 m^2 dialyser [7,36]. At first the dialysis was still performed extracorporeally on blood withdrawn and then re-infused as a bolus, repeated nine times, rather than continuously as Necheles had done in his dogs. Although the patients improved, the removal of nitrogen (blood urea down from 125 to 50 mg/dl, that is in modern terms a urea reduction ratio (URR, $U_{end}/U_{beginning}$) of 60%) was to Haas 'disappointing'. He was able to observe the diminution in blood pressure and urine output occasioned by dialysis for the first time, as well as ultrafiltration of water from the dialysis circuit, speculating that this might be useful in the treatment of nephrotic oedema [7]: 'Whether its therapeutic use in the treatment of nephrotic oedema is possible will have to be found out in the future'. Summarizing his work in 1928 [7], Haas was cautiously optimistic: 'there have been only three purifications on a grand scale so far—and I know that one swallow does not make a summer.'

Why did Haas abandon his work at this point, and why were there no further attempts at dialysis in humans for 15 years? According to Haas [7,37] a major factor was the ignoring of his work by the medical establishment in Germany, epitomized by the attitude of Franz Volhard (1872–1950), the most distinguished and senior of German professors, with a major involvement in the study of renal disease, who declared at the meeting of the German Society of Internal Medicine in Wiesbaden in 1928 that the technique was of little use because it did not stop renal destruction or promote renal regeneration. Also, it was evident even to Haas, ever cautious and anxious to do no harm, that his patients with advanced irreversible uraemia had not really obtained much benefit from the procedure. Finally, the technique of making fresh membranes for each dialysis was tedious, and fragile collodion was far from being a convenient membrane for clinical use, even if its diffusive properties were appropriate.

Surprisingly, Haas does not seem to have considered the use of temporary dialysis for acute potentially reversible renal failure, as even Abel had considered by now [1]. At that time the concept of acute renal failure was not well developed [38], even though what was later called the 'crush syndrome' had been described first in Germany during and just after the First World War, mercurial chloride anuria was well known and its treatment by peritoneal dialysis was being attempted, and the toxic renal effects of incompatible blood transfusions were just becoming evident (see Chapter 12). However Haas, like Necheles, remained in contact and became aware of the first dialyses performed successfully after the Second World War, although not until 1952—before the news of Kolff's work reached him, such was the disruption in Europe [00]. He also took a lively interest in the chronic dialysis unit set up in Giessen [1].

A new membrane: cellulose

Now with heparin available, the remaining great technical problem of a suitable, really robust dialysis membrane, easily sterilized without damage to the material or alteration in its properties and with long shelf life—on both of which counts collodion performed badly—was solved, outside medicine or even science, by the packaging industry.

Cellulose was coined as the name for a substance which was a major constituent of wood, related chemically to starch, by a committee of the Acdémie des Sciences in Paris in 1839 'a compound which fills the cells and which makes up the substance of the wood itself' [39]. This was one of a number of names ending in *-ose* created by various similar committees at this time, including gluc*ose*. Cellulose itself was first purified from wood in 1885 by Charles Cross and Edward Bevan at the Jodrell Laboratory of the Royal Botanic Gardens at Kew in London [39]. In 1908 Joseph Brandenburger regenerated cellulose acetate in sheet form; this became available from1910 from the Société Industrielle de Thaon in France, under the name of '*cellophane*', and was widely used for packing . Fagette [40] reviews in detail early descriptions of this material during the 1920s. It had been used for laboratory studies of dialysis in sheet form from about 1927, when Freda Wilson of the University of British Columbia pointed out how easily it could be sterilized, in contrast to collodion [41]. Then, in the late 1920s, this

versatile and cheap product was made into tubing for the manufacture of sausages by the Visking company of Chicago. It was tough, did not burst under moderate pressures and even in its commercial form was relatively free of microscopic holes. Almost immediately this sausage skin was used in laboratory dialysis experiments by Andrus [42] in 1928, and it proved to have excellent diffusion characteristics.

Here we see again developments in materials, remote from clinical medicine, which opened possibilities for dialysis. From 1930 to 1939 many papers (reviewed by Fagette [40]) were published on the physical and dialysis characteristics of various forms of cellulose membranes in the chemical and industrial literature.

During the 1930s also, the co-discoverer of insulin in 1923, Charles Best (1899–1978), set out in Toronto, Canada to use clinically the purified heparin. This was prepared by Arthur Charles and David Scott in 1933–1934 [43], with the clinical team led by surgeon Gordon Murray (1894–1976), whose name will reappear shortly in this book as a pioneer of haemodialysis itself. Murray and his colleagues were able to show that heparin could be used prophylactically against deep vein thrombosis (clots in the veins of the legs, see below)—a major landmark in medicine as this and its associated pulmonary emboli (clots breaking off and travelling in the blood stream to impact in the lungs) was a random and much feared, often fatal complication of many types of surgical operation (see Chapter 9).

This newly purified and standardized heparin came to the notice of a New York haematologist working in the convalescent serum laboratory of the New York Public Health Institute, William Thalhimer (1884–1961) (Fig. 7.5) [39,44]. Thalhimer played

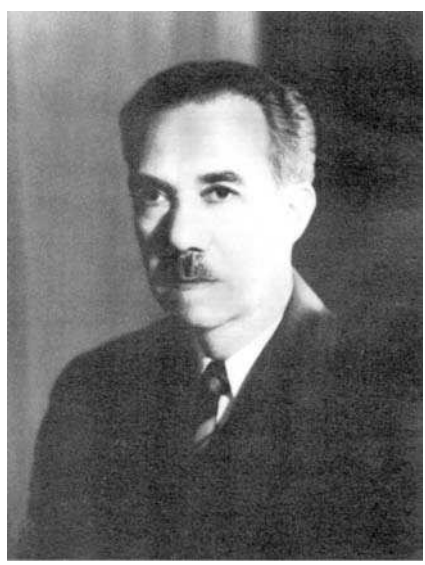


Fig. 7.5 William Thalhimer (1884–1961), the little-known New York haematologist who introduced cellulose tubing into clinical dialysis and thus, together with the use of heparin, made its practical application possible. (Courtesy National Library of Medicine, Washington.)

a pivotal role in the history of haemodialysis, but has received little or no attention from historians of nephrology. Thalhimer had graduated from the Johns Hopkins Hospital in 1908, where he was a pupil of Abel, amongst others, and then worked in laboratories in New York, Milwaukee and Chicago before returning to New York in 1936. Drukker [1] states (without giving a source) that Thalhimer saw a demonstration of Abel's dialyser 'when he was a medical student at the Johns Hopkins University' but this cannot be exact in view of his graduation date; perhaps this event took place later during a subsequent visit to Hopkins. Thalhimer visited Toronto and remained in contact with Best's team. Some of his main interests were blood storage and exchange transfusion, and he used heparin to permit exchange transfusion for alleviation of uraemia in nephrectomized dogs [44]. He then went on to construct an 'artificial kidney' using cellulose tubing 2 cm wide and 30 cm long in an Abel-type kidney to dialyse the dogs [44] and using the Toronto heparin as an anticoagulant. The dialyses lasted 3–5 hours, and up to 1.5 g of urea could be removed. Thalhimer's vital contribution to the evolution of haemodialysis was the realization that commercially available cellophane tubing could be used for *in vivo* dialysis:

> these preliminary experiments suggest the possible use in humans … however this human application should not be made until further investigation, which is now under way in collaboration with Professor C.H. Best.

This fascinating note suggests that Gordon Murray may have got the idea of constructing a dialyser in 1940 in Toronto from discussions between Thalhimer and Best, and later Murray himself mentions Best alongside Abel and Thalhimer as having 'embarked on similar investigations' [44]. The following year the work with Best, on plasmapheresis rather than dialysis and in dogs rather than humans, was published [45].

However, we can see how knowledge of heparin was transferred one way, and of cellulose tubing the other, between New York and Toronto. Thalhimer, in a footnote, says he was unaware of the work of Necheles and Haas until he was writing up his own data. He does not quote any of the laboratory work on *in vitro* dialysis using cellophane, his main emphasis being on the use of heparin: he notes merely that he obtained his cellulose tubing from the Visking company. Why he did not pursue investigation of the artificial kidney further is unknown, but he must have known of Murray's work in developing an artificial kidney in Toronto [46], and perhaps thought of these studies in a collaborating laboratory as the outcome of his own work. He retired from the serum laboratory in 1944, and from consulting haematology in 1950.

Thus, at last, with the availability of standardized pure heparin and cellophane tubing off the shelf, the scene was set for effective dialysis in humans. In retrospect one could predict that the 1940s must see the development of *practical* haemodialysis, and that it would probably evolve simultaneously in several different institutions and countries, given that the information and the rather small technical resources needed were widely available. The only surprise is that this next development did not take place in the United States, as Europe was again plunged into war by the time the decade began—although Canada played its role, as we shall see in the next chapter, and there was an attempt to perform haemodialysis in Philadelphia in 1944.

Fagette [40] suggests that the developing knowledge of the forces of diffusion and flow was a powerful influence in determining when dialysis began: 'no medical technology before its time'. I find this argument unconvincing, as does Peitzman [48]. At no point do any of the pioneers of *in vivo* dialysis quote a single paper from the large mass of work on diffusion through membranes in the laboratory in any of their publications, and the way they approached their laboratory and clinical experiments shows they must have been largely ignorant of this body of work. It seemed that the knowledge that urea, the principal solute accumulating during uraemia, could be dialysed through collodion or cellulose membranes was enough to satisfy them that they were on the right track. Only the lack of an easily used membrane and anticoagulant held back progress from 1920 to 1940, and when these appeared, clinical dialysis followed. Invention, not science, was the prime force.

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very long action (15–20 hours) and failure of antagonism by the heparin antagonist protamine, whilst making it better for prophylaxis against clots, means it is not useful for haemodialysis. Thus the original compound of Howell and his colleagues still reigns supreme in dialysis after 70 years.

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Chapter 8

The first practical haemodialysis machines: Kolff, Murray and Alwall

However primed by the availability of suitable materials, the introduction of machines and successful peritoneal dialysis to treat clinical renal failure required men of great imagination, foresight and above all unusual toughness, given the powerful forces arrayed against them in the medical establishment of the day. Pioneers of dialysis were regarded as mavericks—perhaps even dangerous men—by their colleagues for more than two decades. The first of these unusual men was a tenacious and talented Dutchman, Willem Johan Kolff.

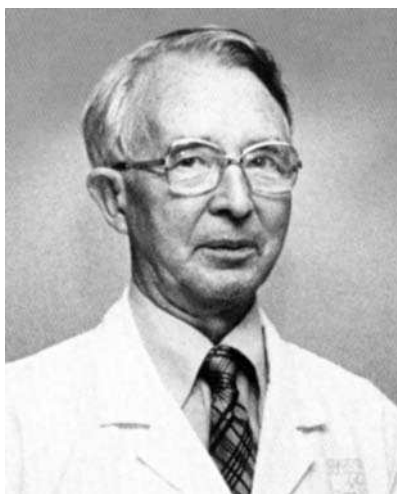
Willem Kolff

The well-known story of Kolff's struggles in war-torn Holland to build and use an artificial kidney have achieved, over the years, the quality of an epic. Even looking at these events in the cool light of history, it is an extraordinary story which deserves its retelling and its reputation. Nowhere were the effects of the war in Western Europe felt more than in the Netherlands: invaded early in May 1940, and liberated late, the Nazi occupation lasted 5 long years. At that time Willem Johan ('Pim') Kolff (b. 1911) (Fig. 8.1a), was working in the department of medicine at the university of his natal town, Gronigen in the north of the Netherlands. Kolff's father Jaap had run a tuberculosis sanatorium, but the young Kolff did not want to be a doctor at first, having seen his father's frustration with failures and fear of seeing patients die, and preferred zoology. However, he changed his mind and qualified in medicine at Leiden in 1935. During his final year of medical school, unusually for a medical student or even a young doctor, he married and his first position at Gronigen was unpaid—the only post he could find that would appoint a married candidate, such were the professional attitudes of the day. Initially he was supported by his wife who came from a relatively wealthy family.

This opposition to the idea of married junior medical staff was widespread in Europe at the time, including Germany, and in the United Kingdom until the 1960s, as I can attest personally. The idea of a 'monastic' group of young men, resident in the hospital and entirely devoted to the care of their patients was strong (women doctors were few in numbers and most medical schools did not admit them until 1940 or even 1950). Later, perhaps, these young doctors could marry—preferably a nurse—or even better the daughter of a senior colleague, to advance their careers. This background is

(a)

(b)



(c)

Fig. 8.1 The three simultaneous creators of the practical artificial kidney in the 1940s: (a) Willem Kolff of Gronigen and Kampen, the Netherlands (b. 1911), (b) Gordon Murray of Toronto, Canada (1894–1976), and (c) Nils Alwall (1906–1986) of Lund, Sweden. Each derived the idea of a dialyser independently of the other, once the materials were available to make dialysis possible. ((a) courtesy Dr Kolff; (b) courtesy Cardiovascular Museum, University of Toronto; (c) courtesy Dr Alwall.)

worth elaborating to give one some idea of what Kolff had to contend with in bringing radically new ideas into medicine in 1930s' Holland.

In charge of just four medical beds he was exposed—as all physicians were until the 1960s—to the helplessness of watching young patients dying horribly and slowly of chronic uraemia, then essentially untreatable [1,2]. Kolff has often recalled one particular patient, a young man to whose mother he had to give the bad news, and who was relieved to hear that her son did not have cancer; Kolff could not bring himself to tell her that the sentence of death from kidney failure was equally final. Unlike other physicians, however, the young Kolff—like Haas before him—determined to do

something about it, and went to the Professor of Biochemistry at Gronigen, Dr Robert Brinkman (1894–1994), who told him about cellophane and his own laboratory use of it for dialysis of blood, encouraging and collaborating in Kolff's early studies. We do not know if Brinkman was already aware of Thalhimer's work. Kolff was the right man at the right time, as he himself modestly acknowledged [1]:

> Since I had both heparin and cellophane, all that remained was to build a dialyzer of sufficient capacity to make the application clinically worth while.

This was in 1938. First he and Brinkman conducted experiments in the laboratory to determine—for the first time—all the quantitative parameters necessary for successful dialysis of a human being. They confirmed that urea could be removed most efficiently using agitation of large volumes of saline dialysate together with agitation of the blood, and attempted to calculate the exact requirements for a kidney large enough to dialyse urea effectively from a patient [2]. This had never been done before, since Haas had used dialysis empirically with regard to its potency.

Then the Nazis invaded in May 1940. Shortly after the occupation, Kolff's professor of medicine, a Jew, committed suicide with his wife [1]:

> personally I owe him a great deal. Instead of forcing his ideas upon his pupils, he made great efforts to follow us when we wanted to pursue a new project. Whereas most other members of staff had shown a marked impatience regarding my plans about an artificial kidney, Polak Daniels had allowed me to go ahead without ridiculing the idea.

A Dutch Nazi was appointed to head the department. On the day he arrived, Kolff left for the small town of Kampen in the centre of the country. Kolff had stopped there previously on his way from the Hague, where he had been when the Germans invaded, and learned that the authorities in Kampen wished to set up a medical service. In Kampen,

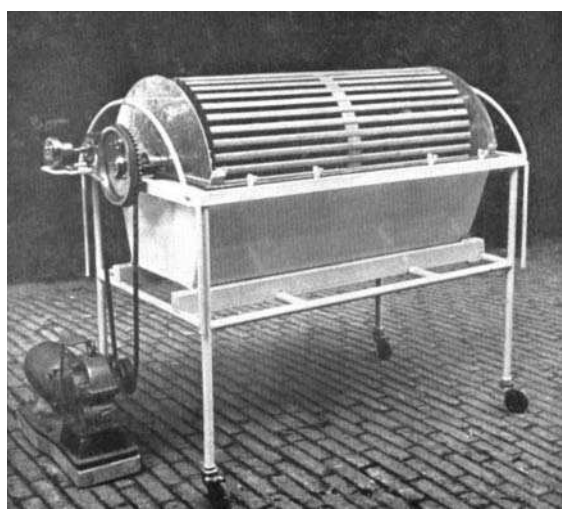


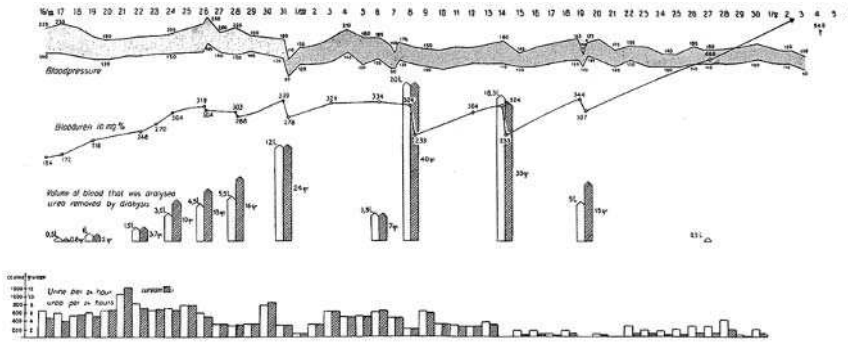
Fig. 8.2 The 1944 version of Kolff's rotating drum kidney with its static open dialysis bath. (From [7].)

Kolff was the only internist at the hospital, but he had asked for—and got—a laboratory and support team. Together with Hendrik Berk, head of the local enamel factory and a practical engineer, he went on to design and constructed a 'dialyser with a large surface area' whose design has become one of the icons of nephrology (Fig. 8.2) [3–7].

This type of pumpless, rotating drum kidney, with 20 m of cellophane dialysis tubing wound round the wooden drum (only later was metal available in sufficient quantities), sitting in an open enamel dialysis tank, and a coupling based on a Ford car water pump to allow blood access to the rotating cellophane tubing, was the standard in clinical use for the next 10 years. It continued in use into the 1960s in some units—including even for some of the early long-term regular dialyses for irreversible renal failure, such as at the Hôpital de la Pitié in Paris [8]! Its design predicated the features shown again, following Hess and McGuigan's work of 1914 [9], to be important in *in vitro* dialysis: good mixing of fluid in both the blood and dialysate compartments. Kolff's cellophane ironically came from Germany—from the Kalle company in Wiesbaden [1]. The other materials Kolff scavenged from wherever he could. All metal was commandeered for use in the Nazi war effort, so the metal used came largely from a shot-down bomber. The rest of the apparatus was made from wood wherever possible. Between them, Kolff and Berk falsified affidavits to obtain materials, which were then used for the artificial kidney; an offence for which either might have been shot.

Unlike his contemporary pioneers (see below), Kolff never did any animal studies, and thus moved into clinical dialysis 2 or 3 years before they did: essentially all these three researchers had a period from 1942 to 1945 during which they improved and modified their apparatus during experimental dialyses, but in Kolff's case this was done in humans and not dogs (Murray) or rabbits (Alwall). Kolff's first patients, an old man called Gustav Boele, with uraemia from prostatic disease (Fig. 8.3(a)) and a young woman with 'malignant' hypertension[1] suffering from contracted kidneys, were cautiously dialysed in February and March 1943; the first was dialysed only once, but the second received 9 dialyses in all. It has been largely forgotten that in these early dialyses Kolff performed intermittent withdrawal and then re-infusion of blood after dialysis, as Haas had done at the beginning of his experiments. Subsequently, with growing confidence, dialysis was continuous, using flowing blood in patients first in Kampen and then on other patients in the Hague and Amsterdam. Worsening conditions in the Netherlands, culminating in a punitive food blockade by the Nazis which led to widespread starvation, together with mass deportations, led to interruptions in the programme from 1944 to 1945. After 16 patients had been treated, and after the liberation of Holland on 11 September 1945, the first patient whose life, Kolff felt, was undoubtedly saved by dialysis underwent treatment—ironically a Nazi collaborator who had been imprisoned in the local barracks. She was a 67-year-old woman called

[1] High blood pressure which had entered a vicious circle of kidney damage, leading to hypertension, and this in turn to more kidney damage. At that time this could not be stopped and always resulted in the death of the patient—hence 'malignant'. Today this state is more usually called 'accelerated' hypertension and can be reversed by medicines.



(a)

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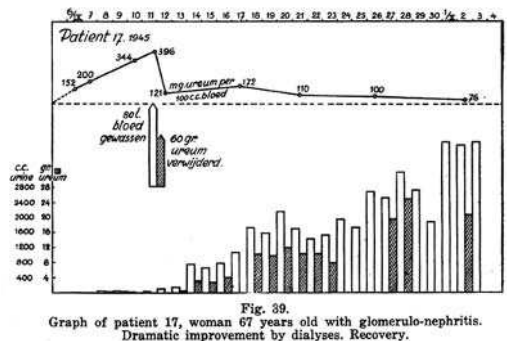


Fig. 39.
Graph of patient 17, woman 67 years old with glomerulo-nephritis. Dramatic improvement by dialyses. Recovery.

(c)

Fig. 8.3 (a) Chart of the second patient dialysed using the fractionated dialysis technique on nine occasions over a month from 16 March 1943. She was Janny Schriver, a young woman of 29 years who had terminal chronic renal failure with accelerated hypertension. However, only 2.5 years later did Sofia Schafstadt (b) survive, generally supposed to be the first patient to achieve this with the assistance of the artificial kidney. She was photographed in October 1945 4 weeks after her illness and dialysis (courtesy Kolff, from [1]). (c) Looking at the chart published by Kolff [7] it appears she might have survived anyway, but Kolff has emphasized that, suffering septicaemia and sulphonamide anuria, she was moribund at the time of her dialysis and improved greatly after it.

Sofia Schafstadt who had cholecystitis, septicaemia and sulphonamide crystal anuria, who recovered and lived a further 7 years (Fig. 8.3).

Kolff's early work was, despite the privations of the war, published in 1943 not only in the Netherlands [3] but also the next year in English in Scandinavia [4] (where

from his own testimony we know it came to the attention of Nils Alwall, already actively dialysing animals), and finally in France [5]. Kolff was clearly determined that his work should be noticed despite the Nazi occupation. At the end of the war Kolff published an expanded version of his thesis [6] in a now classic monograph (Fig. 8.4) [7] which circulated widely and had a major impact on those interested in kidney failure. It is interesting to reflect now what would happen today if a new, potentially hazardous treatment were tried for so long and so unsuccessfully; Kolff later recollected in response to this question that 'no-one ever tried to stop me' [1]. This initial lack of success arose largely from the fact that to begin with, as he had intended, Kolff treated patients with irreversible renal failure; but by 1946 he had realized [1,10] that:

> in cases of chronic (irreversible) uraemia there is in general no indication for treatment with the artificial kidney. However temporary aggravation of chronic uraemia caused by intercurrent infection, diarrhoea or surgery could benefit from a dialysis to tide the patient over the critical period.

Already major problems with access were evident: Kolff used needles or tapering glass cannulae in artery and vein, tying the vessel off after use, and then re-inserting it a little further up for the next dialysis. The machine was connected to these cannulae by precious red rubber tubing—almost unobtainable because of the war—re-used for each dialysis after careful cleaning and sterilization. Some of the acute patients who had had repeated dialyses but still remained anuric eventually ran out of access and

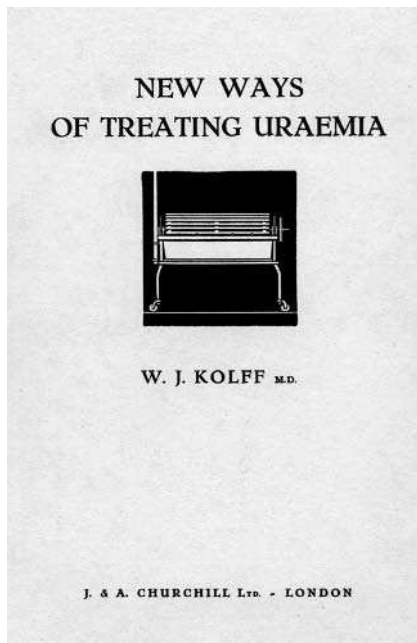


Fig. 8.4 *New ways of treating uraemia*, 1947 [7]. After this book the management of acute uraemia was utterly changed, but only after a period of scepticism (see text).

could no longer be treated, an observation that was to be repeated over and over in other settings.

As the war ended and communications opened up, Kolff not only gave detailed plans and drawings of his kidney away, but also constructed more than a dozen machines, many of which were given away and shipped to various parts of the world, as discussed below. Kolff never attempted, then or since, to make any money out of his major contributions to medicine, and he has remained a major critic of the costs of dialysis as usually performed today.

His design proved remarkably durable, especially considering that it had a number of major mechanical and biological disadvantages (as Kolff himself was only too aware) and by 1956 even he himself abandoned it. These difficulties included the fact that large amounts of heparin were required to keep the blood in the dialyser from clotting, which led to major problems with haemorrhage in some patients during and after dialysis, which dogged all the early pioneers using his type of apparatus. This particular problem was improved when Kolff realized that metal was even more thrombogenic than glass or cellophane. Also the cellophane dialysis tubing, although generally robust and supplied without tiny holes in it, punctured easily both during assembly and the dialysis itself. The volume of blood in the circuit outside the body was large and variable, leading to abrupt falls and rises in blood pressure, which the sick patients tolerated badly. Pressures in the blood circuit became very high during dialysis, leading to uncontrolled filtration of fluid squeezed from the blood in the circuit—a fault soon rectified by Mark Joekes in England (see Chapter 11). The bath of dialysate, being open, evaporated so that the concentration of salts altered. The tubing had to be wound for each dialysis onto the drum before dialysis could begin, and this process was tedious and time-consuming. Finally, when the patients were connected, all contemporary accounts mention the severe rigors (shaking attacks with fever) that almost all patients suffered. Nevertheless, even this crude design was effective as it had a large surface area available for dialysis (over 2 m^2), and it spawned modified versions which gave it a total effective life of over 20 years.

Kolff was not alone in trying to build an artificial kidney, although much less attention has been paid to his two co-pioneers, especially in the United States, which became Kolff's home from 1950.

Gordon Murray

Independently, the cardiovascular surgeon (Donald Walter) Gordon Murray (1894–1976) of Toronto, Canada (Fig. 8.1b), already a pioneer of the clinical use of heparin as noted above, performed the first successful haemodialysis in North America in Toronto on 6 December 1946. He was helped by another surgeon from Edinburgh, Edmund Delorme [11], together with a chemistry undergraduate, Newell Thomas [12,13]. Their patient was a young woman with acute renal failure, which although contemporary public accounts described as suffering from 'complications of pregnancy' was in fact the result of an illegal abortion (which was then not available in any country except under extreme circumstances). The benefit of long experimentation on animals in the laboratory was evident, and this first patient recovered after three sessions of dialysis.

Murray [14–20] was born on a farm in Western Ontario on 29 May 1894. His father was a Scottish stonemason who emigrated to Canada to farm, and his mother was Canadian. The rather austere family background encouraged observation, education and betterment, and in 1914 Murray enrolled into Toronto University to study medicine. However, the First World War intervened, and he spent the next several years in the army, seeing service in the trenches in France, during which he was wounded and was mentioned in despatches for bravery. Graduating in 1921, after 18 months in rural practice, he decided to train in London in 1923, taking the London FRCS qualification before returning to New York, and then home to Toronto in 1928 where he married, took up an academic appointment, and also started a very large and successful private practice.

A multitalented individual with a restless, enquiring mind and a brilliant technical surgeon, Murray's career presents many interesting problems for the historian. He appears to have been difficult as a person for his colleagues (although much revered by his students [14,16]) and something of a 'loner'. Finally, his successful work was almost forgotten in the aftermath of some flawed behaviour late in his career. Clarke in his generally adulatory article [16] described his colleague as a 'brilliant maverick' but also 'not one to underestimate himself'—perhaps because his experience, ability and training were so much greater than almost all his colleagues in Toronto. As well as his work on heparin in cardiovascular surgery during the 1930s with Best, which led to his landmark papers on the use of heparin to prevent deep vein thrombosis after surgery [21,22], later he performed the first replacement of an aortic valve in 1955 using a homograft [23] (a prepared natural valve rather than a mechanical one) as well as a number of other innovative cardiac surgical procedures. He studied vascular grafting using autologous veins and arteries in 1948, and also used transplantation to treat nephrectomized animals as early as 1933 (see below), as well as performing some of the earliest renal transplants in humans in 1951.

The links between Thalhimer and the Toronto unit through heparin [24] have been mentioned in the previous chapter, so that Murray was well aware of the potential of cellophane, as well as being an expert on heparin. Murray's first clinical success with haemodialysis in 1946 came following extensive work in dogs, begun as early as 1940. In these experiments he ingeniously created a controlled uraemic state by implanting their ureters into their bowel, so that the urine was reabsorbed into the body from the gut. He made many modifications in the design of the dialyser over these years. The story that the dialyser was built in Gordon Murray's basement at home can be discounted [25], but it is true that all the work was done with money raised by Murray himself, some of it from his own pocket; in his letters he quotes a figure of $10 000, a considerable sum in 1940. Murray noted tartly [13]: 'otherwise the work was carried out independently of the university or other assistance' as he usually did at the end of many of his papers. Nevertheless, the traditional view of physicians and surgeons who liked tinkering with machines as the basis for dialysis was established early in its history, as Peitzman [17] has pointed out.

Finally Murray and his colleagues settled on a design of a narrow (6 mm) cellophane tubing (to maximize surface area) up to 50 m long, wound round a static vertical wire mesh drum through which dialysis fluid was pumped—an early coil

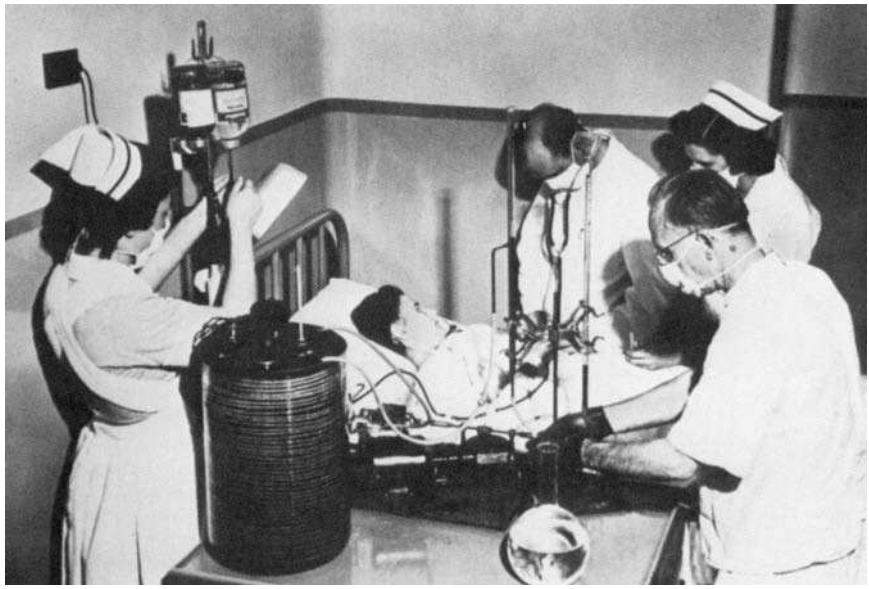


Fig. 8.5 The Murray coil kidney (left) in use in 1947. Unlike Alwall's similar coil design, there was no closed outer jacket. Murray himself is on the right. According to Dr Cairdwell (centre picture), this scene was posed for photographic purposes and does not show an actual dialysis in progress (personal communication from Dr S McKellar, Toronto). This photograph, credited to Gus Pasquarella, first appeared in the *Saturday Evening Post* of 28 January 1950.

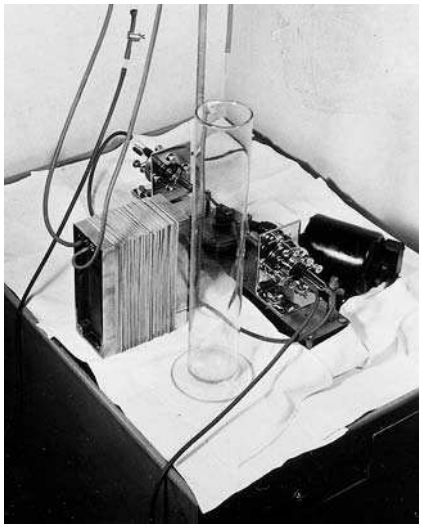
kidney (Fig. 9.5). The design was not very powerful —much less so than Kolff's—as judged by the figures for urea clearance given by Murray, but this could easily have been solved by scaling the machine up. However, the absence of major moving parts such as in Kolff's machine was a huge advantage. They used a vein-to-vein blood circuit, because of the need to sacrifice arteries for repeated dialysis, which meant he had to design a special pulsatile blood pump which produced minimum breakdown of red blood cells, to move blood from the main vena cava to a peripheral vein. Evidently oblivious of a multitude of papers from previous decades, to begin with they used pure water as a dialysate, which inevitably led to breakdown of the blood cells passing through the machine; but eventually they settled on a balanced salt solution with a total concentration about that of blood plasma, similar to that used in peritoneal dialysis and by Kolff.

The published accounts [12,13] of Murray's work are not detailed, and he was always careless in reporting properly on many aspects of his work. Often in his writings it is not clear how many patients were treated, or how long they were followed up; details are sketchy at best, a major fault for any scientific clinician. For example, it is difficult to establish even how many patients were dialysed in Toronto, since all his three major papers give details only of three early cases, although Murray mentioned a '50% success rate' in 1949 [13]. However, from other sources [26,27] (which indicate

also the wide public interest in the new treatment at the time) it can be pieced together that altogether 11 patients were dialysed by Murray between 1946 and 1949, with five survivors, and a further five were treated up to 1951. Few patients were referred, because the treatment was regarded in Toronto with great suspicion and at best only as a desperate measure, to be undertaken only in patients already dying, so Murray's results were respectable in the light of parallel experience with Kolff's rotating drum model. Murray was invited to lecture in London in 1949 and as well as lecturing on the surgical treatment of congenital heart disease, he delivered the Alexander Simpson lecture on the artificial kidney and its use [13]. This aroused much interest, despite, perhaps because of, the fact that dialysis was in abeyance in the United Kingdom at that time (see Chapter 12). In 1949 also Kolff came to Toronto and met Murray during a visit to the United States.

It is not entirely clear why he stopped using the machine, even given the indifference and indeed active opposition of the medical establishment in Toronto. Clarke [16] writes that the machine was abandoned because staff were not available to run the dialyses, and so Murray himself had to be present throughout the whole of dialysis, as Kolff was in all his treatments. Kolff was a physician and this was his main interest: Murray was a busy general surgeon with a private practice to maintain, which financed his work. Also his interests were turning again to cardiovascular surgery at this time. After 1951 there was a gap of a year or more during which Murray did no dialysis.

Clarke [16] describes and illustrates a parallel plate dialyser (Fig. 8.6a), parts of which are now on display in the Cardiovascular Museum in Toronto. This advanced and much more efficient dialyser was designed and built in 1952–1953 with Dr Walter Roschlau, who had come to Canada from Heidelberg in 1951. The design of these machines is discussed in Chapter 12, but is even simpler than the static coil dialyser. Flat sheets of cellophane are sandwiched in a frame to form a stack, in which alternate compartments allow blood and dialysate to flow usually in opposite directions to increase the efficiency of the exchange. This machine is even more simple to use, and more compact than the coil kidney. Roschlau maintains that he did not know of the similar Skeggs–Leonards and MacNeill designs of the late 1940s (see below) [28], but we do not know if Murray himself was aware of these. The new Toronto dialyser was evaluated carefully in dogs, but used on only two patients in 1953. It was used, however, much more extensively in Europe—unfortunately with some rather unsavoury undertones. A German engineer, Erwin Halstrup, had been employed by Roschlau to do some work on the flat plate kidney. Halstrup left to return to Europe, taking the designs with him without the knowledge of Murray or Roschlau, and after his return to Germany Halstrup offered the Murray–Roschlau kidney for sale as the 'Halstrup Nephra I' kidney (Fig. 8.6b). This version was used in at about 35 patients in Freiburg in 1953 to early 1956 [29], but was rather too small. A larger, 1 m^2 version—the 'Nephra II' (Fig. 8.6c)—with plexiglass plates was contructed by Halstrup and was used in Göttingen (Dr Bohn), Marburg (Dr Bock), Bonn (Dr Gutgemann) and Tübingen. However, even in Freiburg it was then abandoned for the twin-coil design, or the local Möller version of the Alwall kidney (see Chapter 12), despite the advanced design and efficiency of the Halstrup kidney.



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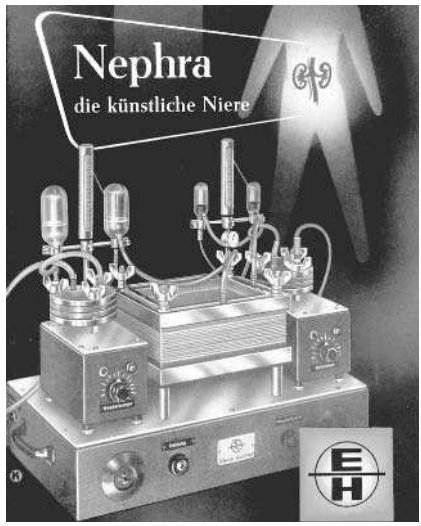

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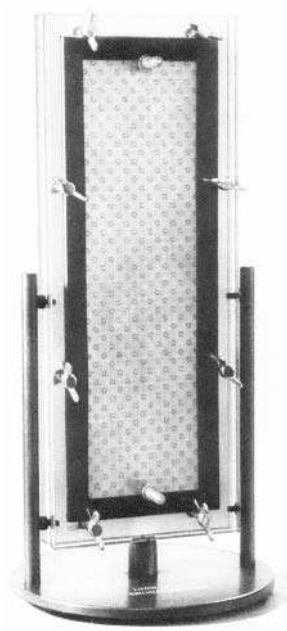

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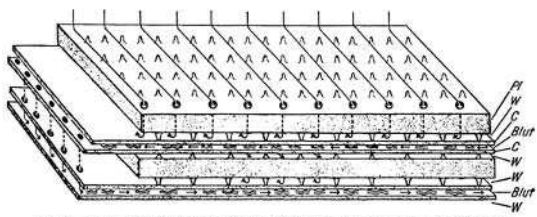


Abb. 3. Detail der künstlichen Niere Freiburg: 2 Blutkammern und 3 Waschkammern.
Pl = Kunststoffplatte; *W* = Waschflüssigkeit; *C* = Cellophan.

(d)

Fig. 8.6 (a) The now forgotten Murray–Roschlau flat-plate kidney. This was used at least once in 1955 to treat a patient in Toronto, but later it was used without Murray's permission in Freiburg and elsewhere in Germany as the 'Halstrup Nephra I' dialyser (b). (c) The more sophisticated Nephra II was used in several units in Germany. The illustration from the Halstrup catalogue (which is the same as one used by McBride in his book [30]) is in fact of a small version, only 30 × 16 cm, for laboratory use, as is shown by the fixed baseplate; but the drawings (d) and description show that the much larger clinical dialyser had the same basic construction. It came in 0.6 m^2 and then 1.0 m^2 versions, with plexiglass plates (an advanced feature) and even multipoint supports (see text).

Only 10 years later were flat-plate dialysers to achieve this degree of sophistication (see below). A now forgotten but important feature of the Murray–Roschlau design was that it incorporated, not a grooved but a multipoint membrane support, the cellophane sheets being supported by plates with rivet heads (cones in the Halstrup version) thus increasing both dialysate turbulence and the area in contact with the membrane, a feature which became standard in high-efficiency parallel-plate dialysers in the 1970s. Drukker [10] and most other commentators erroneously attribute this type of dialyser design to later work in New York in 1960, even though the Halstrup version is illustrated in McBride's book [30]—although without any commentary in the text.

The effect of Halstrup's actions on Murray, who discovered this deceit only when letters arrived from Germany asking about his experience of his own kidney, was disastrous, and he did no further work on dialysis. He did, however, attend the inaugural meeting of the American Society for Artificial Organs (ASAIO) which was founded in 1955, but went there in relation to his cardiovascular work.

It is worth noting in brief that Murray was concerned also during this period with transplanting kidneys. He studied organ preservation, autotransplantation and homotransplantation in animals during the 1930s, and finally in man, first as temporary grafts attached to arm vessels, and then full cadaver kidney transplantation in four patients during 1951 and 1952 [31], using the external iliac vessels. As usual Murray's accounts of these operations are sketchy: three of these patients died, but one survived 35 years without any immunosuppression. It is impossible to know whether the transplanted kidney or recovery of native kidney function contributed to this, and Murray performed no more transplants after 1952, even when interest in the area became widespread towards 1960.

Murray's natural independence, and his independent funding at the W.P. Caven Research Institute in Toronto, meant that less and less was his work subject to any sort of review; as we have noted repeatedly, he had always been careless of long-term follow-up and neglected giving detailed description of procedures or even full results. After his work in cardiac surgery, Murray again became restless and moved to new fields, which led to controversies which dogged him at the end of his career. First, he became interested in immunotherapy using an anticancer serum in the late 1950s. This he made in his laboratory and used, although it is not clear what the results were. To be fair, the immunological aspects of cancer were much in the news then and since, but Murray's casual approach to this complex problem did nothing to enhance his reputation. Then in the 1960s he began treating paraplegia surgically, by re-anastomosing the spinal cord. Finally, he claimed results which could not be substantiated, and was finally asked to take early retirement in 1966—he was after all now 72 years of age. He survived a further 10 years, seeing the success of renal transplantation and long-term dialysis, both of which he had helped to pioneer.

It is difficult not to view Murray's flawed career with sadness. For a long time Toronto wished to forget him because of the circumstances surrounding his retirement, and only recently have attempts been made to rehabilitate his memory and recognize his undoubted achievements, which include the independent development of successful clinical dialysis. Also, the design of his artificial kidneys were much

superior to Kolff's gigantic and clumsy rotating machine thrashing in its open tub. Kolff himself abandoned his own design, and turned to a similar apparatus to Murray's for his disposable 'twin-coil' dialyser of 1956—the success story of that period (see Chapter 12). The flat-plate dialyser he and Roschlau designed was the forgotten prototype for the majority of the dialysers used during the 1970s and 1980s. His use of the vena cava for blood access for dialysis was also years ahead of its time.

At least two machines based on the Murray coil design were used elsewhere at the same time as their use in Toronto, and there is mention in articles in the popular press [26,27] of several other Murray machines in Buffalo, the Mayo Clinic, Tel Aviv, New Delhi, Cape Town and Beijing. I have not yet been able to obtain details of these. However, the first documented use outside Canada was by another cardiovascular surgeon, an acquaintance of Murray's, Conrad Lam (1905–1990) (Fig. 8.7). Lam was a Texan who had worked on heparin, like Murray, and together with Joseph Ponka in the Henry Ford Hospital in Detroit [32] performed the first haemodialyses in the

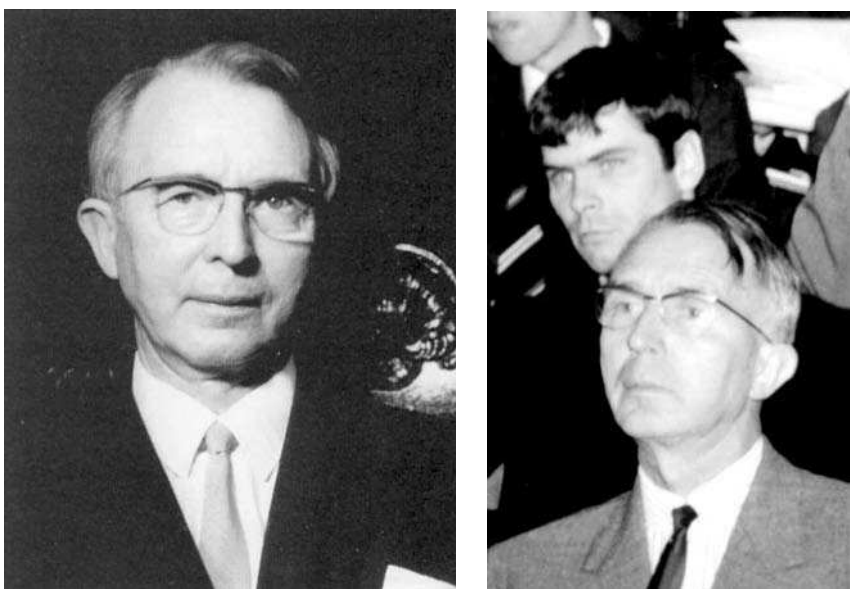
Fig. 8.7 Conrad R. Lam (1905–1990), a cardiovascular surgeon at the Henry Ford Hospital, Detroit, who performed the first tentative dialyses in the United States in 1947 using a Murray-type kidney, but did not follow this up. (Courtesy Henry Ford Health System Archives, Detroit.)

United States in 1947 (if work in Philadelphia in 1944, discussed in Chapter 11, is discounted). This work in Detroit has been almost completely neglected in subsequent histories (although quoted quite frequently in contemporary papers) in favour of later work in New York and Boston, perhaps because the clinical experience was brief and relatively unsuccessful. After studies in 10 nephrectomized dogs, two anuric patients were dialysed by Lam and Ponka, but only once each, with problems from bleeding from the heparin; both patients expired, and no further studies appear to have been performed despite active encouragement from Murray [33].

The second Murray-type kidney was built and used by Tito Ribeiro de Almeida (1913–1998) in São Paulo in Brazil from 1949 onwards [34,35], who thus performed the first haemodialyses in Latin America (see Chapter 11). A further Murray kidney was in the Sinai Hospital, Baltimore in 1945–1946 [36], but there is now no record of its having been used. This was before Murray himself had used it clinically.

Nils Alwall

The third pioneer of the artificial kidney was Nils Alwall (1906–1986) (Figs 8.1c and 8.8) [37–39] working in Lund, Sweden, a country which remained neutral during the war, and thus did not suffer the ravages of the rest of the continent, but which during this period was effectively cut off from the rest of the scientific world. Alwall was born



(a) (b)

Fig. 8.8 (a) Alwall as President of the International Society of Nephrology 1975–1978. (b) Alwall and the author (rear) in the audience at the founding meeting of the EDTA (European Dialysis and Transplantation Association) in Amsterdam, 1964. Later Alwall was President of the EDTA, also, in 1970.

into a farming family as Nils Andersson in Kristianstad, southern Sweden in 1906, and was educated locally [38]. Having worked from 1926 as a physiologist, pharmacologist and biochemist in nearby Lund, taking his PhD with a study of thyroid function and nitrophenols, in 1935–1936 he spent a year in Pécs in Hungary as a pharmacologist; this was to be his only direct foreign contact outside Scandinavia until 1948 [39]. In 1927 he changed his name from Andersson to Alwall [38]. At the end of the 1930s, by now already in his early thirties, he decided to enter clinical medicine and was appointed assistant professor in 1940 with renal disease as one of his main interests, finding its treatment completely unsatisfactory [39].

As early as 1942, Alwall had constructed a flat-plate dialyser (now in the Museum of Medical History, Lund [39]) (Fig. 8.9) before fixing, as Murray had done, on the design of a static vertical coil kidney of cellophane tubing (Fig. 8.10). As with Murray's kidney, this design had considerable advantages over the Kolff design. The rotating coupling through which blood had to flow was eliminated, resulting in a considerable reduction in heparin doses, but the principal innovation was that in Alwall's design the container holding the coil and dialysate was closed, and not open as in Murray's design. This enclosed coil minimized hypotension when blood was run in to it, as the tubing expanded much less than the unsupported coils of Kolff's or Murray's open dialysers. Moreover, controlled ultrafiltration of fluid from the blood was immediately possible. Only in September 1946 after extensive testing in animals, mostly rabbits, were versions of this machine first used on a patient [39–41]. This early clinical experience met the same initial high death rate as Kolff—although his second

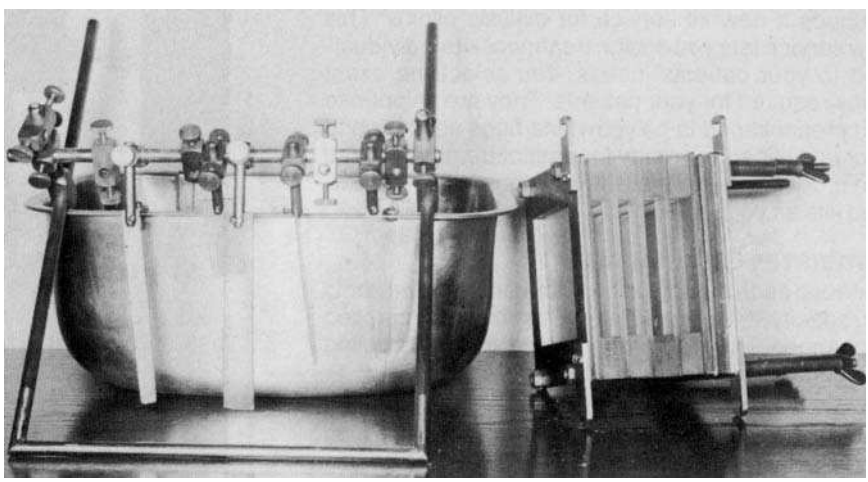


Fig. 8.9 Alwall's experimental flat-plate kidney of 1941–1942; several of the modules shown in the picture were connected together. This model did not work well, and after trials in animals Alwall abandoned this for his jacketed coil design, on which he did trials in animals from 1942 to 1946, before performing his first dialyses in humans that year. Even in 1941 Alwall was already using materials such as plexiglass, as well as older materials such as rubber.

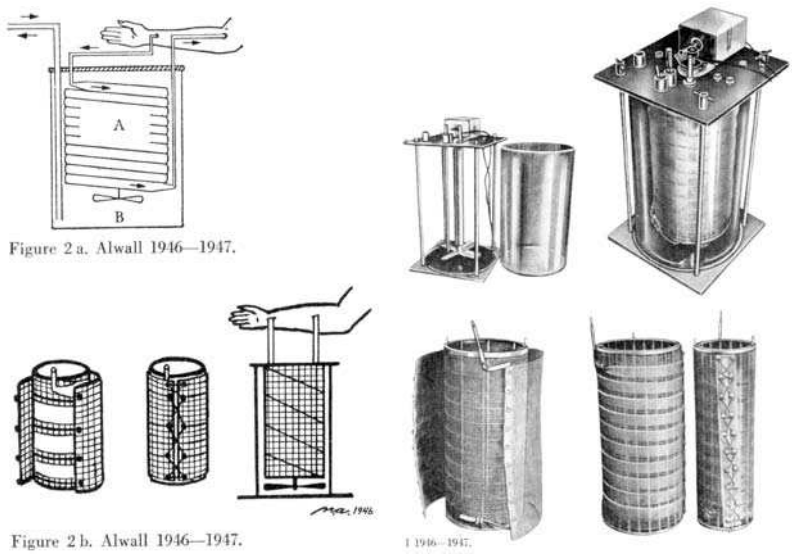


Fig. 8.10 (a) Alwall's sketch design for a coil kidney, and (b) the kidney itself. Like Murray's, it was mounted vertically but also had a closed steel jacket which permitted controlled ultrafiltration, a crucial advance in dialysis technology. However, it made the unit very heavy and clumsy to use. (From [95])

patient, a woman with an exacerbation of chronic glomerulonephritis, did survive long term. In 1986 he wrote [42]:

> after several years of animal experiments we were finally allowed to perform our first treatment in a moribund patient in 1946. As an associate professor I depended on the permission of the director of our medical department, who feared the new method. The general opinion was adverse.

This was a very different experience from the indifference that Kolff met with, and similar to the opposition encountered by Murray; nevertheless, despite the inevitable death of the first patient, the ' irresolute' professor was sufficiently impressed [39] to support further trials, and the second patient survived.

Perhaps because of his modest, methodical and quiet character Alwall has never received the credit he is due: not only as a pioneer of dialysis [42,43], but of controlled ultrafiltration, arteriovenous shunts (see Chapter 14) and renal biopsy [44]. He published some 40 papers on the treatment of acute renal failure by dialysis from 1946 to 1963, when he summarized his experience in a massively detailed—but almost unreadable—book, which lacks an index [45] but contains an invaluable historical bibliography of dialysis in the 1940s and 1950s. The unit he founded dialyses patients today after 55 continuous years of operation—a unique achievement in the world.

Unlike the rather abortive work in Canada, it is little appreciated today that the Alwall kidney was used successfully for some time in about 50 units, mainly elsewhere

in Europe, from the 1940s to the early 1960s [45], starting with one in Copenhagen and another in Cracow, Poland in 1947 (Dr Z. Hanitski) and in Haifa, Israel in 1948 (Dr Kurt Steinitz) [46]. Two machines were even used, albeit briefly, in the United States in 1954–1955 (one by Dr T.S. Danowski [47]), and the first dialyses in Australia in 1956 were done by Drs David Edwards and H.M. Whyte using an Alwall kidney [48]. These units were generally phased out only when the twin-coil model was introduced 10 years later, because in practice the Alwall kidney was not easy to use. Its massive outer casing was very heavy, and the coil was difficult to wind and mount without puncturing the tubing—a problem with all the early dialysers that required winding before use. Nevertheless, it continued in use in the Lund unit well into the 1960s [45], until the flat-plate disposable kidney developed by Alwall together with A.B. Gambro was introduced (see Chapter 12).

In 1947 came the first contacts between Alwall and Kolff by correspondence, and Kolff sent Alwall Visking cellophane tubing to try. In 1948 Kolff came to Stockholm and Lund, and met both Alwall and Bodo von Garrelts who was working on a coil dialyser (see Chapter 12). Alwall also took his kidney to dialyse abroad, including a visit to Oslo and another to Guy's Hospital in London at Easter 1948 [49], by which time dialysis in London had ceased temporarily. This visit was probably occasioned by an article summarizing Alwall's experiences to date, published in the *Lancet* in January 1948 [50], which brought his work to a much wider audience than his many papers published previously in Scandinavian journals, even though they were in English.

Conclusions

It is interesting to look back over this chapter and compare these three pioneers of the artificial kidney, so different in their backgrounds, characters and achievements—although it is true that both Murray and Alwall came from rural farming stock with a strong religious background. Alwall, in strong contrast to Murray, recorded his results in meticulous and sometime pedantic detail, as his book of 1963 demonstrates. In the public mind there is no doubt that Kolff (apart from his priority in time over the other two with regard to dialysis in humans) is widely regarded as the 'inventor' of the artificial kidney, which must be considered to some extent as a misreading of history. The prolonged animal experiments which both Alwall and Murray—but not Kolff—were able to perform, postponed Alwall and Murray's application of the treatment to humans by several years. Thus, unlike Kolff's long period of trial and error before a successful dialysis could be reported, both Murray and Alwall independently were able to report successful dialyses almost immediately they moved into the clinical field. I have tried to indicate that the construction of such a machine was almost inevitable at some time during the 1940s—as Kolff himself agreed. What remains surprising, given Thalhimer's work, was that it was not first constructed in New York! In fact there was an unrecorded attempt to construct a dialyser from cellophane tubing by Jonathon Rhoads and Henry Saltonstall in Philadelphia in 1944, in ignorance of all the work being done outside the United States (see Chapter 11) [51].

It is interesting also to speculate what would happen were dialysis to be introduced as a potential new technology today. Certainly, extensive animal work would be

demanded before its application to humans. We know now that dogs are particularly difficult to keep alive on regular dialysis, mainly because of coagulation problems (the early work was done on single dialyses to show the removal of urea and salt balance, and not for survival); such a programme would almost certainly be judged a failure. As we shall see in Chapter 11, it had been known since 1936 that cellulose would activate the complement system in the blood leading to an inflammatory response, and further study of the *in vitro* interaction would almost certainly lead to a demand for 'biocompatible' membranes that did not lead to inflammation or coagulation of blood, before use in humans could be contemplated. The use of urea as a surrogate for unknown toxic substances would probably have been judged as invalid, and identification of more specific uraemic toxins and demonstration of their removal required. The costs of development and testing of prototype devices would be colossal, and require major investment by researchers and by industry, as well as major intervention by government agencies on the safety of the treatment.

How different from the 1940s, when Kolff could say 'nobody ever tried to stop me'; empiricism had the major role—and patients no voice.

Notes and references

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Chapter 9

Peritoneal and intestinal dialysis after the Second World War

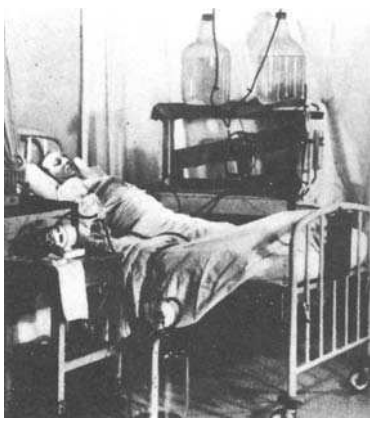
Peritoneal dialysis

In contrast to work on haemodialysis, in which three successful artificial kidney machines were developed at different sites during the conflict of the Second World War, almost nothing was done or published on peritoneal dialysis during this period. However, at the end and immediately after the war a number of workers re-examined the possibility of treating acute, potentially reversible renal failure using dialysis from body cavities: of these intestinal dialysis had some impact initially, but peritoneal dialysis proved most successful and was pursued more vigorously. In part, this surge in the development of peritoneal dialysis was brought about by the emergence of the concept of a syndrome of 'acute reversible renal failure', in addition to the long-recognized chronic irreversible forms of kidney disease; this is a story we shall deal with in Chapter 10.

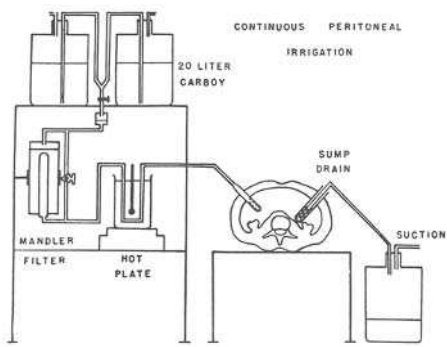
The most important work on peritoneal dialysis at this time was done in the Department of Surgery of the Beth Israel Hospital in Boston, in part under a grant from the national Office of Scientific Development and Research (OSRD) and by the Department of the Navy to examine means of treating battle casualties with temporary acute renal shut-down [1–3]. This programme was under the direction of Jacob Fine (1900–1980) and his associates surgeon Howard Frank and chemist Arnold Seligman (Fig. 9.1a). The fact that these investigators were working in a surgical department may have led to the fact that much of the work in peritoneal dialysis over the next 5 years or more was done in departments of surgery also. Their careful and systematic analysis of the physiological problems in dogs [3], and success—in that one of their first four patients with acute reversible renal failure survived treatment [1]—did much to establish peritoneal dialysis as a treatment useful in buying time for these patients, and their series of papers are a poorly recognized major landmark in the history of dialysis.

Their first successful outcome came in 1945 [1], just about the same time as Kolff's much more famous first successful haemodialysis (see Chapter 9), in a 51-year-old man whose renal shut-down was brought about by blockage of the renal tubules with insoluble sulphonamide crystals. Their initial system used two rubber whistle-tip urethral catheters to ensure good drainage of the instilled fluid—still a problem and often leading to fluid overload—with the sterilized dialysis fluid in 20 L Pyrex glass carboys, thus permitting a closed system and prolonged dialysis without changing the bottle. The dialysis fluid was a modified Tyrode solution (Table 9.1), used for physiology perfusions, which mimicked the composition of plasma but contained more

(a)



(b)



(c)

Fig. 9.1 (a) Surgeons Jacob Fine, Howard Frank and Arnold Seligman of Boston, who in 1945 dialysed a patient with acute renal failure who recovered (from McBride [3]). Their apparatus (b) and a diagram (c) of the circuit they used for continuous peritoneal dialysis though two catheters. Their work over the next 3 years was influential in persuading many (especially surgeons) in the United States and elsewhere that peritoneal dialysis was a viable option for the treatment of acute renal failure (From [1]).

sodium (156 mmol/L) and less bicarbonate (12 mmol/L)—both of which deviations turned out to be adverse. This solution was run in and out continuously using rubber tubing as connectors. The patient was dialysed continuously for 4 days before renal function returned, and he was the first patient to recover from intrinsic acute renal failure with acute tubular necrosis, as Wear's patient of 1938 [4] had had urinary tract obstruction. Three other patients were not so lucky and did not survive.

Fine and his colleagues continuously experimented and improved their system on a trial and error basis; their papers are very frank about what they did wrong and what

Table 9.1 Early peritoneal dialysis solutions

	Ringer*	Hartmann†	Rhoads 1938	Fine‡ (mod. Tyrode) 1947	Abbott§ 1947	Derot 1947	Kop 1947	Grollman 1951	Maxwell 1959 ('Dianeal')
Na^+/mmol/L	156	104	251	139	131	131	131	139	141 (142/146)
K^+ mmol/L	4	4	3	2.6	5	0	3	4	3.5
Ca^{2+} mmol/L	4.5	4	3.5	1.1	5	4	5	4.5	3.5
Mg^{2+} mmol/L	–	–	–	1	1	0	–	1.7	1.5
Cl^- mmol/L	162	101	255	141	114	114	113	113	101
PO_4H^{2-}	–	–	–	1.1	1.1	–	1.1	–	–
CO_3H^- mmol/L	2.4	–	–	12	26	26	26	36	–
Lactate	–	3.1	'2.4 ml'	–	–	–	–	–	45
Glucose g/L	–	–	–	1.5(10)	10–20	22	10–30	10	15/65 (15/70)

Ganter used 134 mmol/L (0.8%) saline for his single exchange in 1923. Balázs and Rosenak in 1934 used 42 g/L dextrose solution for one dialysis, and 134 mmol/L (0.8%) sodium chloride on two other occasions.

Other authors (1946–1950) generally used either Fine's modified Tyrode solution or one of the two solutions developed by Abbott and Shea. Reid in England was alone in using twice physiological saline (1.8%), i.e. 295 mmol of Na+ and Cl; for his first two patients, before changing to 'normal' (isotonic, 0.8%) saline for the third, and also using isotonic glucose alone.

† Used by Smith and Eaves 1947.

‡ Several slight modifications were introduced by Fine and his colleagues in 1946–1948; they increased the concentration of glucose to 10 g/L in later solutions, and also used gelatin 10 g/L. Tyrode itself has 156 mmol/L of sodium, not 139 mmol/L.

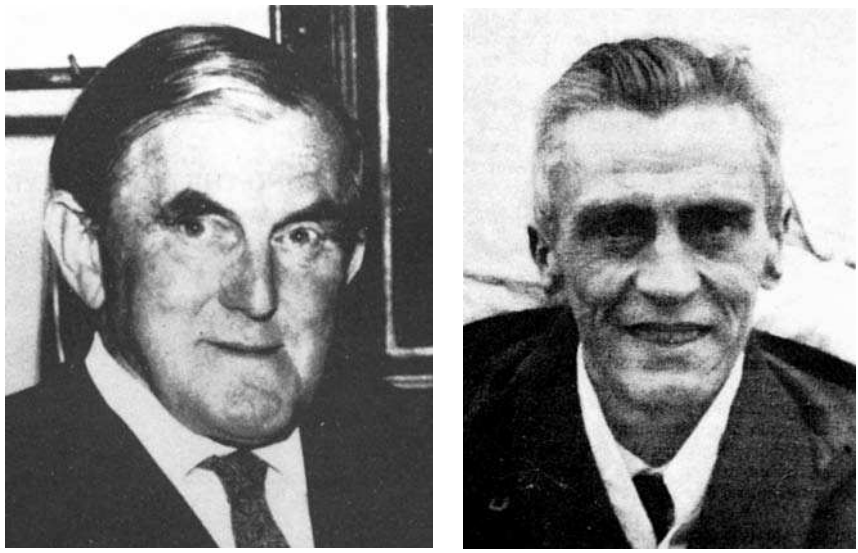
§ Abbott and Shea described several modifications of their solution 'A' and solution 'P'. The main difference were that solution 'P2' contained less potassium, calcium and magnesium than the solution 'A' shown here, and contained sodium citrate as well as sodium bicarbonate to buffer it.

they learned from their mistakes. Later they lowered the concentration of sodium to 7.4 g/L (125 mmol/L) [3], used a specially designed double-lumen sump drain catheter, added gelatin 1% to a concentration of glucose which they established should be 2 g/dL to prevent accumulation of fluid, and up to 10 g/L of glucose to remove excess water. They added the gelatin as well as glucose to remove water by osmotic gradient, because 'glucose alone in sufficient amount is possibly too irritating'—probably as a result of caramelization of the sugar, a problem that was to haunt peritoneal dialysis for the next two decades. They also tried intermittent as well as continuous drainage. By the 1948 report [3], they had accumulated four survivors out of 18 patients treated, of whom five at least had chronic irreversible disease. Only six patients escaped peritonitis, predominantly from *Escherichia coli* infection. Then across the street in the Brigham Hospital, John Merrill and his colleagues began using the Kolff haemodialyser under George Thorn's direction; Frank took up thoracic surgery and Seligman left for the Johns Hopkins Hospital and this most productive team broke up.

In the same month as the first paper from Fine's group at the Beth Israel Hospital (March 1946), William Abbott and Lieutenant Patrick Shea of Cleveland, Ohio published a similar detailed analysis [5] of work on dogs made uraemic by nephrectomy. Abbott and Shea used large needles to infuse fluids of varying composition. They rapidly abandoned isotonic (5%) glucose solution, as it caused concentration of the blood, and acidosis because of a shift of salts and bicarbonate into the dialysis fluid. They recommended finally a solution which they called solution 'A', which substituted bicarbonate for the lactate in Hartmann's solution, but otherwise resembled it closely, with the addition of dextrose 10–20 g/L. More importantly they were perhaps the first to point out the advantages of intermittent as opposed to continuous dialysis, but their advice was generally ignored for another 5 years. Their paper, along with that by Fine and his colleagues, formed the scientific basis for peritoneal dialysis during the next decade.

Many of the problems associated with peritoneal dialysis arose from difficulties with the fluids used. After using peritoneal dialysis themselves in 1947, Howard Odel and Deward Ferris of the Mayo Clinic summarized in a massive and important article of 1948 [6] the many different fluids that had been used to date in a review of their own and others' experiences. Metabolic acidosis and overload were a common association using isotonic saline, or the Locke–Ringer and modified Tyrode solutions, which mimicked the composition of normal plasma, but contained insufficient bicarbonate or lactate to correct the mounting acidosis of the uraemic patient with no renal function, and too much sodium. At that time they were able to review the treatment of 15 patients with potentially reversible disease treated up to the end of 1947, of whom eight survived.

In the first use of peritoneal dialysis in the United Kingdom, Ronnie Reid (Fig. 9.2a), a urologist in Colchester [7], and his colleagues actually used a salt solution with twice as much sodium as in the plasma and no bicarbonate at all, administered through a Foley urethral catheter. They dialysed, in March 1946, a 36-year-old woman who had received a mismatched blood transfusion and had gone into acute renal failure, with anuria lasting 12 days. She was treated for 2 days using cycling infusions with a 2-hour



(a) (b)

Fig. 9.2 (a) Urologist Ronnie Reid, who performed the first peritoneal dialysis in the United Kingdom in Colchester, Essex in 1946 (courtesy Dr Frank Parsons). (b) Physician and chemist Pierre Tanret (1909–1965) who co-ordinated an extensive programme in Paris between 1946 and 1950 in the unit of Maurice Dérot at the Hôtel Dieu in Paris, and performed the first peritoneal dialysis in France, again in 1946 (from [13]).

dwell period and then drainage, and recovered—the third patient in the world to survive using peritoneal dialysis. Reid continued working on peritoneal dialysis over the next 2 years [8] and treated a further five patients, two of whom had irreversible disease with two of the other three surviving. However, Reid gave up using peritoneal dialysis in 1948, partly because he was sceptical of the role played by this new treatment:

> This is just a brief account of my experience with peritoneal dialysis, and the results are not impressive … What have we gained from the experience? There is no doubt that clinical improvement occurs which cannot be translated into clinical terms … peritoneal dialysis is in its infancy. It may one day be the most potent weapon in our hands for the treatment of uraemia and may even be extended to the relief of other toxaemias.

However, according to one of his colleagues he gave up partly under the influence of the papers from Graham Bull discussed in the next chapter. Interestingly, when their first patient arrived in March 1946, Reid and his colleagues were unaware of the scattered previous work on peritoneal dialysis and went ahead from scratch; Fine's papers had yet to appear. A surgical renal biopsy was obtained during renal decapsulation on this patient. A further patient was biopsied at the insertion of a nephrostomy tube, and this time sulphonamide crystals blocking the renal tubules were demonstrated [8]. These are probably the first renal biopsies done in patients

with acute renal failure, as previous biopsies had all been in children and adults with glomerular diseases [9]. Unlike in the United States (as we shall see), surgeons and physicians in the United Kingdom did not follow Reid's pioneering work: the next British paper on peritoneal dialysis that I can identify was not published until 1962, again from a urologist [10].

Only Wear and his colleagues [4] had by that time made use of the more physiological Hartmann's solution for dialysis, which had a lower sodium level (130 mmol/L) and more bicarbonate (28 mmol/L) (Table 9.1). Piet Kop in the Netherlands [11], working with Kolff, used a custom-made solution closely resembling it, but with the addition of 10–30 g/L dextrose. Odel and colleagues themselves developed a custom-made solution ('P') with 140 mmol/L sodium and 24 or 36 mmol bicarbonate, together with 10–120 g/L of glucose. There were problems also with sterilizing solutions containing bicarbonate, which had to be added just before use—hence the substitution of lactate, which is converted to bicarbonate in the liver after infusion. It was more than a decade before the fluids for use became standardized and then commercially available (1959), and all hospitals where peritoneal dialysis was being done had to make up and sterilize their own fluids. This was not such a burden in those days, however, as many large hospitals routinely had to manufacture their own fluids for intravenous infusions, but was a major disincentive to undertaking peritoneal dialysis for those that did not have this facility. This situation persisted well into the 1960s.

Clinical results began to accumulate during the mid and late 1940s in Europe as well as in the United States. In the Netherlands from July 1945 to 1947, Kop and Kolff [11] had treated a total of 13 patients, using a closed system very similar to that of Fine and colleagues (Fig. 9.3), except that the Berk enamel factory supplied the containers for the dialysing fluid. They added 30 g/L of glucose to this only if the patient accumulated oedema. Heparin was added to the fluid through the (rubber) inflow tube because they were impressed with the high protein content of the fluid emerging, as noted first by Engel as long as 20 years before. Trocar catheters were used for access. Three of the first five patients with acute renal failure survived, but none of the further eight with chronic renal disease did [11]. However, McBride [12] notes of Kop's data that 10 of altogether 21 outcomes were successful, as detailed in Kop's thesis [11], which is not an easy volume to access. Details of only two of these patients are available in Kolff's monograph [11] and Kop never published his results in full outside of his thesis in Dutch, and this substantial amount of work is often overlooked in favour of Fine and his colleagues.

In France important advances were also made in the unit of Maurice Dérot (see Chapter 11, Fig. 11.2b) in Paris with a clinical chemist Pierre Tanret (1909–1965) (Fig. 9.2b) [13] in charge of the programme. Their work has received little attention hitherto [13,14] and none at all in the United States—McBride never quotes their work, nor do contemporary reviewers such as Odel and Ferris. Even Drukker does not cite any of their papers. Initially, the group in Paris [15] were unaware of the work of Putnam and Ganter; Fine's and Abbott and Shea's papers had only begun to appear; and in this pioneering situation the group met with little success. However, their later technique [16] employed solution 'A' of Abbott and Shea (but without the magnesium

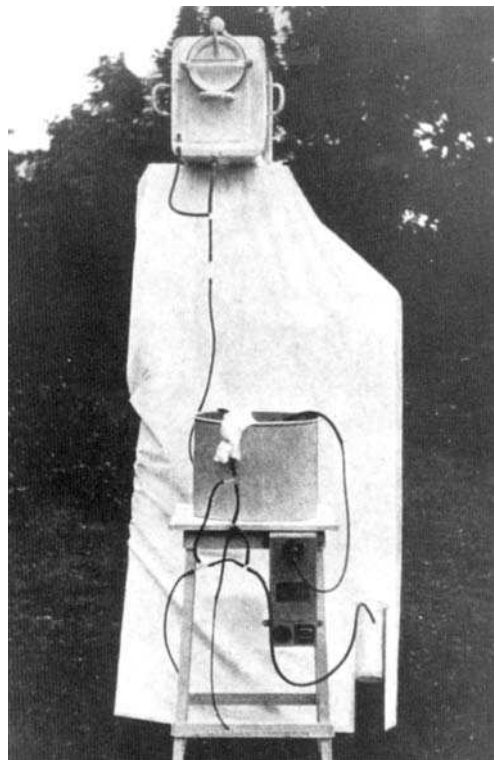


Fig. 9.3 The peritoneal dialysis system of Piet M.S. Kop, who with Kolff used peritoneal dialysis at the end of the Second World War to treat patients with acute renal failure. (From Kolff WJ. *New ways of treating uraemia*. Churchill, London, 1947.)

and phosphate), and short intermittent dialysis. Between 1946 and 1949 the unit treated 64 patients with acute renal failure from various causes—a total equal to the whole effort reported from all the rest of the world. The causes of the renal shut-down are interesting to review in the light of subsequent changes in epidemiology of acute renal failure: abortion (32), mercuric chloride poisoning (16), sodium chlorate (2) and intoxication (Table 9.2). Details of most of these patients are given in the 1951 thesis of Marcel Legrain [16], but interpretation of the outcomes in those treated with peritoneal dialysis (26 recoveries from 38 patients, a remarkable 68%), is complicated by the fact that the majority (31) also received exchange transfusions of large volumes of blood. This treatment had some currency in France at that time, having been used in acute anurias by a number of clinicians [17] including Pasteur Valléry-Radot [18] and Jean Dausset [19]. However, of the seven patients treated by peritoneal dialysis alone, five survived, a similar proportion to those who were given no specific treatment (eight out of nine) or exchange transfusion alone (10 out of 17).

Dérot's group was also responsible for introducing one of the first purpose-built metal catheters (designed by Jean-Charles Reymond) which had a double lumen, mul-

Table 9.2 Causes of acute renal failure requiring dialysis, 1948–1950: some large series.

Diagnosis	Odel et al., 1946–50	Legrain, 1951 (Paris)	Swan & Merrill, 1952 (Boston)	Total
Transfusion reaction	14	5	19	38
Post-abortion	0	32	2	34
Mercury poisoning	12	16	2	30
Postoperative	6	2	18	26
Haemolysis*	3	3	13	17
Sulphonamide intoxication	10	0	2	12
Carbon tetrachloride	2	1	7	10
Shock from volume depletion	0	0	10	10
Toxaemia of pregnancy	5	1	1	7
Obstruction	6	0	0	6
Haemorrhagic shock	1	0	3	4
Acute nephritis	2	1	0	3
Trauma	0	0	3	3
Sodium chlorate	0	2	0	2
Burns	0	0	2	2
Alcohol	2	0	0	2
$CuSO_4$ + chloroform	0	0	0	1
Phosphorus poisoning	0	0	1	1
Pancreatitis	0	0	1	1
Acute hepatitis	0	0	0	1
Penicillin sensitivity	0	0	1	1
Unknown	0	3	0	3
Total (recovery)	63 (32)	64 (44)	82 (44)	209 (114)

Note that a single main cause of acute renal failure has been attributed in each patient, whereas in about one-third of cases there were in fact multiple contributing causes.

* Haemolysis occurred from prostatic bed irrigation with distilled water (10) blackwater fever (2) and other causes of haemolysis (7).

tiple small perforations to avoid entry of omentum, and a flat plate for attachment to the abdomen. In addition they were probably the earliest to recommend a flexible catheter with side perforations made of the new material polyethylene, in 1949 [16], as Arthur Grollman was to suggest 2 years later. Stephen Rosenak, now at the Mt Sinai Hospital in New York, designed and used a purpose-built metal cannula for peritoneal dialysis which incorporated a flexible tip made of a spiral stainless steel coil [20] in an attempt to provide multiple outlets as the tube flexed (Figure 6b, Chapter 6).

Elsewhere, in Algiers, Edouard Benhamou realized the possibility of using the technique as an ultrafilter to remove salt and water in oedematous states by employing hypertonic dialysis solutions. This was used to relieve the oedema of both the nephrotic syndrome without uraemia [21] and chronic heart failure [22] with some success, as J. Schneierson [23] had advocated in the United States the previous year.

In addition to these large and more systematic programmes in France, the Netherlands and in Boston, many case reports appeared of isolated or occasional patients being treated for anuria with peritoneal dialysis from 1947 to 1949 [24]. These attempts, which occurred largely in the United States and most frequently in urological or surgical units, were almost certainly provoked by the publications of Fine and his colleagues. An early success (in 1946) was that of Goodyear and Beard [25], and another notable report amongst these early papers was that of Smith and Eaves of Minnesota [26], of whose four patients three survived acute renal failure from incompatible transfusion, sulphonamide anuria and obstructive uropathy. The number of published papers dealing with peritoneal dialysis was four in 1946, 19 in 1947, 15 in 1948 and 19 in 1949, indicating the widespread interest in its use. As early as 1948 the technique was used to dialyse an infant [27], whilst haemodialysis was first used in children only in 1954, so far as I can establish (see Chapter 11). Odel and Ferris published in 1950 a further valuable landmark review of the literature from 1923 to the end of 1948 [28], finding by this time records of 101 patients who had received peritoneal dialysis (but excluding, as before, the extensive work in France). Sixty-three of these patients had potentially reversible kidney failure, of whom 32 had recovered, an encouraging rate of 51%, which allowed them to conclude that peritoneal dialysis had a place in the treatment of acute anurias. As we shall see, however, not all were convinced this was true, and today we would be more concerned with the role of publication bias in these figures, which probably represented a maximum achievable. In medicine as in life, those who fail rarely publicize their failures, whilst success is always marketable. It is interesting again to note the similar pattern of causes for the reversible acute renal failure in the patients in this review (Table 9.2); here the largest group (14 patients) followed haemolysis after incompatible blood transfusion, whilst 12 suffered poisoning by mercury and 10 from sulphonamide anuria; only six cases followed surgery and five complicated toxaemia of pregnancy. We shall return to this topic in the next chapter. Odel and colleagues discussed exhaustively the choice of fluid for dialysis, access techniques and duration and timing of the dialysis.

The final act in this post-war boom in peritoneal dialysis was the work of Arthur Grollman (1901–1980), considered in more detail in Chapter 11. To begin with, as we shall see in Chapter 10, he remained unconvinced of the value of any from of dialysis [29]. However, almost accidentally, he was to play a major role in the development of practical peritoneal dialysis during the 1950s.

Intestinal 'dialysis'

In parallel with the use of the peritoneum went exploration of the lining of the gut as a site for dialysis—intestinal dialysis, also called gastrodialysis when the stomach

rather than the small intestine was used. This technique involved inserting a tube into whatever part of the alimentary canal was to be used, and passing fluid into and out of the lumen of the gut to allow exchange across the intestinal membrane. In the case of the small bowel, a few investigators isolated a loop surgically with two openings on to the skin, so that it could be perfused externally. One cannot strictly speak of 'dialysis' of the gut, since the absorptive membrane of the gut is complex and many layers of cells thick, without vessels exposed underneath a relatively inert membrane, as in the peritoneum and in the pleural spaces in the chest. What actually happens is that the intestinal fluid is removed, and with it any potentially toxic substances that may have passed across the intestinal wall into it. However, we will use this phrase as a shorthand for assisted diffusion by lavage.

The idea was not new even in 1947. Auguste in 1929 explored duodenal drainage in uraemia [30], and a year later in Poland, Marceli Lansberg and Szenkier [31] performed appendicostomies to allow colonic lavage in rabbits made uraemic with uranyl nitrate. In 1932, Pendleton and West demonstrated diffusion or secretion of urea into intestinal pouches in normal and uraemic dogs after nephrectomy [32]. The idea remained fallow throughout the 1930s, but in 1941 Goudsmit again examined 'forced intestinal drainage' as a treatment for uraemia [33] using intraluminal tubes and sodium sulphate, as did Rogers and his colleagues [34]. As well as studying the peritoneum, Jacob Fine and his colleagues in Boston [3] also studied dialysis using loops of bowel in dogs, finding that perfusion of a 25 cm (10 inch) length of ileum was equivalent to about 10% of the dog's renal function. Encouraged by this they also made a single attempt to create and use a similar loop in a human, but abandoned the attempt as the clearance was too low to be useful.

About the same time, Nannie de Leeuw (whom we shall meet again in connection with haemodialysis in Chapter 11) studied intestinal lavage in Kolff's busy and enterprising unit [11]. First, she and Kolff produced appendicostomies in two patients with advanced renal failure and small contracted kidneys who also had severe vomiting. However, the concentration of urea in the perfusate was too low to be useful. In a single uraemic patient with tiny kidneys and accelerated hypertension, a 1 m loop of small intestine was formed surgically, with two ends opening on to the skin. At 1 L perfusion per hour, 0.5 g of urea could be removed. The only problem was scarring and obstruction of the stomata through the skin. The patient died 2 months later at home.

White and Harkins explored this method of treatment in 1947 [35], as did several other authors during the late 1940s [36]. Others, in parallel, examined the possible role of gastrodialysis [37]. Both Eric Twiss in the Netherlands [38] and Jean Hamburger and his colleagues in Paris [39] adopted the method of intestinal dialysis. By the early 1950s intestinal dialysis was in routine use at the Hôpital Necker, and in Twiss' unit in Rotterdam, but elsewhere it was used only sporadically. Twiss collaborated with Kolff in treating one patient using perfusion of an isolated intestinal loop who was maintained for as long as 6 weeks whilst anephric [40]. By 1950, intestinal dialysis seemed to be a technique with a definite future role in the treatment of renal failure, but in retrospect it is easy to see that few patients would tolerate the presence of an intestinal tube and the exchanges of fluid for the better part of every day, which were necessary to achieve useful clearance of metabolites.

Dialysis by other routes

Other body cavities such as the pleura, the lung, the spinal fluid, lymph and even the bladder were explored for dialysis during the 1950s and early 1960s, but these experiments not surprisingly met with little success [41], although as Starling's data (see Chapter 6) had predicted half a century previously, the pleura was a remarkably efficient dialyser in the short term.

Notes and references

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2. Seligman AM, Frank HA, Fine J. Treatment of experimental uremia by peritoneal irrigation. *J Clin Invest* 1946; **25**: 211–19.
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4. Wear JB, Sisk IR, Trinkle AJ. Peritoneal lavage in the treatment of uremia. *J Urol* 1938; **39**: 53–62.
5. Abbott WE, Shea P. The treatment of temporary renal insufficiency (uremia) by peritoneal lavage. *Am J Med Sci* 1946; **211**: 312–19.
6. Odel H, Ferris D. Treatment of acute renal failure by peritoneal dialysis. *Proc Staff Meetings Mayo Clin* 1947; **22**: 305–14; Odel HM, Ferris DO, Power MH. Clinical considerations of the problem of extra-renal excretion: peritoneal lavage. *Med Clin N Am* 1948; **32**: 989–1076.
7. Reid R, Penfold JB, Jones RN. Anuria treated by renal decapsulation and peritoneal dialysis. *Lancet* 1946; **ii**: 749–53. *Renal decapsulation* (stripping or incising of the capsule of the kidney) was still being performed in the 1940s and even the 1950s in a number of renal diseases, its use being particularly persistent in acute renal failure. A number of patients treated by peritoneal dialysis in the 1940s also had this operation done, sometimes on one and sometimes on both kidneys. Alwall's patient who went into renal failure after renal biopsy in 1944 also had it done [9]. I have not encountered it in descriptions of patients treated by haemodialysis, probably because of the danger of bleeding arising from the use of heparin for dialysis if an operation were done. The idea of decapsulation had arisen in 1895 [9] based upon the hypothesis that in nephritides the intrarenal pressure was elevated and needed relief. The treatment was popularized by the New York surgeon George Michael Edelbohls (1853–1908) in his book of 1904: *The surgical treatment of Bright's disease* (Lisietski, New York) and this completely unfounded treatment persisted until it was critically examined in the 1940s. Legrain [16] correctly advises against its use in acute renal failure, but this was as late as 1951! The story of renal decapsulation illustrates the durability of useless and even dangerous treatments in the days before the idea of randomized controlled trials were available (see Chapter 11, ref. [34] for more on controlled trials).
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12. McBride PT. *Genesis of the artificial kidney*. Baxter Healthcare, Chicago, 1987.
13. Anon. Pierre Tanret (1909–1965). *Bull Mém Soc Méd Hôp Paris* 1965; **116**: 1718–24. Tanret's health was poor throughout his life, and this may be why he did not take a career as a front-line clinician, which was obviously his main interest, but became instead a clinical chemist.
14. Tanret P, Reymond J-C. Sur 9 cas de'azotémie grave traitée par l'hémodialyse intrapéritonéale. *Bull Mém Soc Méd Hôp Paris* 1947; **63**: 1059–69.
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16. Legrain M. *Les néphrites aiguës anuriques*. Doin, Paris, 1951. This is an important document, because besides describing Legrain's own experiences it has a valuable and extensive bibliography of papers on acute renal failure and dialysis up to 1950.
17. The use of exchange transfusion as a treatment for uraemia, otherwise than when indicated in cases of intoxication by haemolytic agents such as sodium chlorate, arsine or other causes of massive haemolysis, was almost confined to Paris and persisted for only a few years, from the mid 1940s to the mid 1950s although the earliest reference is to a paper from 1925 (Gilbert A, Tzanck A. Émission sanguine avec restitution globulaire (traitement des néphrites chroniques avec azotémie et anémie). *Bull Mém Soc Méd Hôp Paris* 1925; **49**: 40). See: Tzanck A, Dausset J. L'exsanguino-transfusion dans les anuries. *Bull Mém Soc Méd Hôp Paris* 1948; **64**: 563; Bessis M. *L'exsanguino-transfusion en dehors de al maladie hémolytique de nouveau-né. Acquisitions récentes médicales*. Flammarion, Paris, 1948; Dufour A, Des Mesnards G. Anuria due to acute azotemic nephritis: recovery with exsanguino-transfusion (method of Bessis). *J Urol Méd Chir Paris* 1948; **54**: 602; Lian C, Siguier F, Crosnier J, Savoie JC, Poullain P. Anurie 'post abortum' due au bacilli 'perfringens' guérie par exsanguino-transfusion. *Bull Mém Soc Méd Hôp Paris* 1949; **65**: 265. Isidore Snapper in New York used the technique once or twice in 1952. Exchange tranfusion was used also to treat uraemia in children: Pichot-Janton M, Jézéquel C. Néphrite aiguë infectieuse anurique. Exsanguino-transfusion, guérison. *Arch Franç Pédiatr* 1953; **10**: 1101.
18. Vallery-Radot P, Milliez P, Laroche C, Polonovski Cl. A propos de trois nouvelles observations d'anurie 'post abortum' guérie par exsanguino-transfusion. Considérations sur la pathogénie des néphrites aiguës. *Bull Mém Soc Méd Hôp Paris* 1950: **66**: 454–67.
19. Dausset J. Lower nephron nephrosis. Report of treatment of forty-four patients by repeated replacement transfusions. *Arch Intern Med* 1950; **85**: 416–31.
20. Rosenak SS, Oppenheimer GD. An improved drain for peritoneal lavage. *Surgery* 1948; **23**: 832–33. This has some claim to represent the first attempt to produce a cannula specifically for clinical peritoneal dialysis (see Chapter 6, Fig. 6.7), rather than using one already available for another use. Tanret's use of a polythene catheter was not until 1949, and Grollmans's in 1951 (see Chapter 11) [29].
21. Benhamou E, Albou A, Grigeur P. Oedèmes irréductibles au cours d'une néphrose lipoïdique traités avec succès par la dialyse péritonéale. *Bull Mém Soc Méd Hôp Paris* 1950: **66**: 1293–301.

22. Benhamou E, Albou A, Griguer P. Oedèmes irréductibles au course d'une asystolie mitrale, traité par la dialyse péritoneale. *Bull Mém Soc Méd Hôp Paris* 1950; **66**: 1301–5.
23. Schneierson J. Continuous peritoneal irrigation in the treatment of intractable edema of cardiac origin. *Am J Med Sci* 1949; **218**: 76.
24. See for example: Weiss HA, Mills RL. Treatment of uremia with continuous peritoneal irrigation. *US Naval Med Bull* 1946; **46**: 1745–50; Forminje P. Die behandeling van de acute uremie. *Ned Tijdschr Geneeskd* 1946; **90**: 1184; Bassett SH, Brown HR Jr, Keutmann EH, Holler J, van Alstine HE, Mocejunas O, Schantz H. Nitrogen and fluid balance in treatment of acute uremia by peritoneal lavage. Analysis of peritoneal washings for protein, non-protein nitrogen and phosphorus. *Arch Intern Med* 1947; **80**: 616; Connolly EA, Lempke AW. Peritoneal irrigation in uremia. *Nebr St J Med* 1947; **32**: 387; Grossman LA, Ory EM, Willoughby DH. Anuria treated by peritoneal dialysis. *JAMA* 1947; **135**: 273–5; Muirhead EE, Small A, Haley A, Hill J. Peritoneal irrigation for acute renal damage following incompatible blood transfusion. *J Lab Clin Med* 1947; **32**: 988; Robertson H, Rutherford P. Peritoneal irrigation in the treatment of renal failure due to transfusion reaction. *J Lab Clin Med* 1947; **32**: 982; Strean GJ, Korenberg M, Portnuff JC. Acute uremia treated by peritoneal irrigation. *JAMA* 1947; **135**: 278; Whitlaw DM. Observations on a perfusion method for reducing azotemia in temporary renal failure. *J Clin Invest* 1947; **26**: 1200; Baggenstoss AH. Carbon tetrachloride intoxication treated by peritoneal lavage. *Proc Mayo Clin* 1947; **22**: 321; Buckley RW, Scholten RA. Treatment of acute uremia by peritoneal lavage. *N Engl J Med* 1947; **237**: 431–4; Allbee RH, Mayfield JL. Successful treatment of case of uremia by means of peritoneal irrigation. *Milit Surg* 1948; **102**: 348; Ameline A, Dérot M, Mouret D, Brochen G. Néphrite aiguë anurique probablement scarlatineuse traité avec succès par l'irrigation péritonéale *Bull Mém Soc Méd Hôp Paris* 1948; **64**: 636; Cave WH. Treatment of anuria by peritoneal irrigation. *South Surg* 1948; **14**: 338; Pendino JA, Hampton HP. Peritoneal dialysis in treatment of acute uremia. *J Fla Med Assoc* 1948; **35**: 368; Weistock HL, Nitsche GA Jr. Report of a case of lower nephron nephrosis treated by renal capsulotomy and peritoneal lavage, recovery. *J Urol* 1948; **60**: 577; Localio LA, Chassin JL, Hinton JW. Peritoneal irrigation. *JAMA* 1948; **137**: 1952; Batson R, Peterson JC. Acute mercury poisoning: treatment with B.A.L. and in anuric states with continuous peritoneal lavage. *Ann Intern Med* 1948; **29**: 278; Bonge E, Verflingstad H. Peritoneal irrigation in anuria. *Nord Med* 1949; **41**: 995; Fields JA, Martin HE, Simonsen GB, Wertman M, Etsover L. Treatment of acute anuria with evaluation of peritoneal lavage. *Ann Surg* 1949; **129**: 445; Poulsen JE, Hald H. Intestinal and peritoneal irrigation in treatment of uraemia and anuria. *Ugeskr Laeg* 1949; **111**: 223–6; Selvaag O. Experiences with peritoneal irrigation and intestinal irrigation in uremia. *Ugeskr Laeg* 1949; **111**: 227; Vanderbroucke J, Deleu J. La dialyse péritonéale. *Acta Clin Belg* 1949; **4**: 371; Boulet P, Serre H, Mirouze J. Anurie suivant intoxication mercurielle et traitement avec dialyse péritonéale. *Paris Méd* 1949; **39**: 29; Richet G, Meyer-Heine A, Masse J, Bernier JJ. Néphrite anurique mercurielle guérie après une dialyse péritonéale. Rôle du surrénale dans la désintégration protidique des anuries mercurielles. *Bull Mém Soc Méd Hôp Paris* 1949; **65**: 101; Fenn GK, Nalefski LA, Lasner J. Transperitoneal lavage for twenty-six days in the treatment of azotemia. *Am J Med* 1949; **7**: 35. It can be seen that the great majority of these patients were reported from the United States, with occasional papers from France and Scandinavia.
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39. Hamburger J, Mathé G, Crosnier J. La perfusion intestinale dans le traitement de l'insuffisance rénale aiguë. *Bull Mém Soc Méd Hôp Paris* 1950; **66**: 1716–27.
40. Twiss EE, Kolff W. Treatment of uremia by perfusion of isolated intestinal loop. Survival for 46 days after removal of only functioning kidney. *JAMA* 1951; **146**: 1019–22.
41. See, for example, articles on the *bladder*: Moeller C. Neue Wege in der Behandlung des akuten temporären Nieren-Versagens. *Med Klin* 1949; **79**: 889. *Pleura*: Ganter's work on a single pleural dialysis in 1918 is discussed in the text; De Morais B, De Carvalho S. Pleural dialysis. *Gaz Med Port* 1951; **4**: 423 (this work was in dogs and showed comparable removal of urea through the pleural and peritoneal cavities, as Leathes and Starling's work (see Chapter 6) had suggested would be the case); Lindholm T. Pleural dialysis in a case of acute renal failure. *Acta Med Scand* 1959; **165**: 239 (the patient was treated thus because of gastrointestinal haemorrhage whilst on haemodialysis) ; Shumway N. Pleural dialysis in the uremic dog. *J Urol* 1959; **81**: 567. *Lung*: Salisbury PF, Briggs JN, Hamel NC, Cross CE, Rieben PA. Pulmonary lavage: the use of the lung *in situ* as an artificial kidney. *Trans ASAIO* 1959; **5**: 32–45; Kylstra JA. Lavage of one lobe of untrained unanaesthetised, anuric dogs. *Trans ASAIO* 1960; **6**: 22–31. *Cerebrospinal fluid*: Chambers WR. Use of cerebrospinal fluid system as an accessory kidney: preliminary note and report of case. *Ohio Med J* 1953; **49**: 696–7. *Thoracic duct*: Cronemiller PD, Byran RL, Boerman HR. Thoracic duct drainage in uremic states in man. *Surg Gynec Obstet* 1959; **109**: 355–8. *Cross-dialysis*: Finally, two Italian authors studied the use of cross-dialysis employing a donor mammal, a goat, whose blood perfused the 'dialysate' compartment of a twin-coil kidney and whose kidneys then excreted the dialysed urea and other uraemic metabolites: Pavone-Macaluso M, Anello A. A new method of treating real failure by the extra-renal route, using a mammalian donor. *Lancet* 1959; **ii**: 704–7.

Chapter 10

The rise of the concept of acute renal failure; the flame photometer, urologists and nephrologists

We have seen that both Alwall and Kolff began their work with the clear intention of treating patients with *chronic irreversible* uraemia, who appeared to both of them as the main clinical problem in the 1930s. It is less certain what Murray's original intentions were in 1940–1942, but seems likely he had the same goals—although it should be noted that unlike his two colleagues, his very first case treated in 1946 was a patient with acute renal failure from mercury poisoning, who had a successsful outcome after three dialyses. In fact, as it turned out, for the first 15 years of its existence as a clinical technique, dialysis was used for a parallel group of patients—those with *acute, potentially reversible* renal failure.

Unlike the large numbers of patients dying slowly and obviously of chronic irreversible uraemia, those with what we now call 'acute renal failure' were, until the 1940s, a rather rare and motley group. However, paradoxically their numbers increased greatly as medical technology advanced: acute renal failure can, in general, be thought of as a *product of partially successful treatment*, in that many such patients have first to survive an initial severe assault in order to have this condition. Until 1940, most patients likely to develop acute anuria from renal shut-down died before it could appear. To begin with, the varied causes were not perceived together as a syndrome or group which might have a common treatment. In the 1930s or early 1940s the emphasis was almost entirely on *anuria*, and the idea of 'acute renal failure' as a total syndrome of oligoanuria, with the consequent electrolyte, acid–base and fluid problems, had not yet emerged.

The exact mechanisms within the kidney of the syndrome of acute renal failure remain obstinately obscure [1], despite half a century's intense investigation. Although there are many and varied routes to this state, its clinical manifestations are rather constant. Renal function shuts down, although usually some urine is passed, and *oliguria* rather than complete absence of urine (*anuria*) is usual. However, this urine has, in addition to being inadequate in volume to maintain fluid balance, an invariable composition of about the same concentration as the blood plasma and does not alter according to need, either in volume or composition. Fluid accumulates

according to intake, the concentration of urea and hundreds of other substances normally excreted in the urine accumulate in the blood, with an increase also in the acidity of the tissues, which finally overwhelms the buffering defences of the body fluids and, along with a rise in blood potassium, leads to cardiac arrest. This takes from 3 to 15 days depending on whether the body is breaking down tissue rapidly or slowly, which in turn varies with the cause of the trouble in the first place. Infection and trauma results in greater and more rapid tissue breakdown.

But the diagnosis is not always a death sentence. Repair takes place within the tubules of the kidney, and from 2 days to many weeks later, renal function returns and eventually may attain completely normal levels. Thus, in the absence of treatment, whether the patient dies or not depends on whether or not the accumulation of toxic substances in the blood gets to a fatal level before the diuresis sets in. The more rapidly the concentrations of these toxins are rising, the more likely is a fatal outcome. Sadly, again, after 50 years of work we still cannot identify the exact mechanisms of damage within the kidney or promote the diuresis the patients so badly need. Hence the drive to remove the toxic compounds by dialysis or other means, essentially to buy time for the kidneys to recover spontaneously. Dialysis has no influence in improving the kidney function, accelerating healing or shortening the period of oliguria—indeed there is some evidence that haemodialysis may lengthen it, as we shall see.

First amongst the causes of acute renal failure is shock and low blood pressure (Fig. 10.1). Suppression of urine in *volume-depleted* patients, whether from loss of fluid or of blood [2] must have been known for centuries, and prompted Latta's epochal but little-known administration of intravenous saline to cholera victims in Edinburgh in 1831 [3]. As discussed above, descriptions of acute renal failure from crush injury in the First World War were lost to notice, even in their country of origin, Germany, but were to be rediscovered indelibly in the second world conflict (see Fig. 11.1) [4,5]. This world war brought the problem into a new focus: more than half of the American soldiers who died in anuria and who were discussed in Lucké's influential paper of 1946 [6] died of *major trauma* with or without crush injury. In both the civil and the military sector, better methods of resuscitation with intravenous fluids and blood were introduced, principally in the 1930s and 1940s, which allowed survival and with survival, possible entry into acute renal failure. The crushing of the muscle released protein pigment (myoglobin) from the injured tissue, which Bywaters showed was toxic to the kidney, in his famous work during the London blitz of 1941 [5]. He also showed that fluid is 'lost' internally from the circulation into the injured tissue, producing shock.

As blood transfusion became more common, so also did the consequences of *mismatched transfusions* from errors in testing blood groups. The incompatible blood is broken down and a load of toxic pigment—haemoglobin in this case—is released and filtered through the kidney. This was relatively rare until the Second World War, as little blood was available or given [7]. Schreiner points out that the Korean war was the first in which blood transfusion was used routinely in battle casualties, thanks to the availablity of refrigeration of blood. In addition, as Schreiner and others have discussed (see Chapter 11, p. 140), refrigerated blood has a very high plasma potassium, which could rapidly be fatal in the absence of renal function.

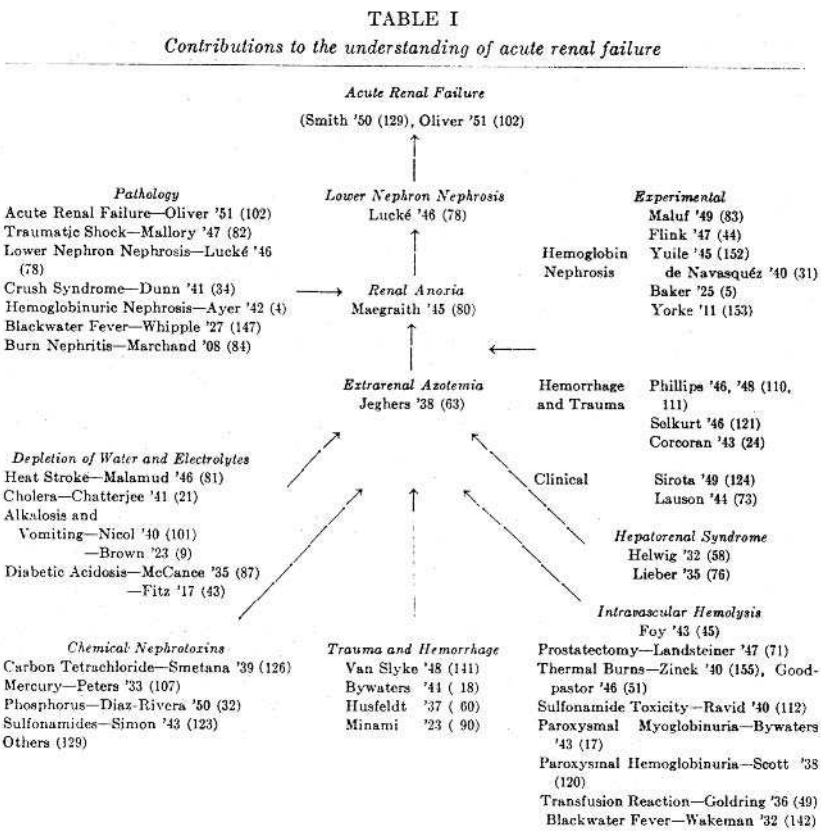

Fig. 10.1 A table from the 1953 paper of Swann and Merrill showing the different elements which came together and gave rise during the 1940s to the idea of a general syndrome of 'acute renal failure', which were thought to have substantially a common pathogenesis. (From [11] with permission.)

Poisoning with mercury had been known since at least the sixteenth century [8], and mercuric chloride poisoning, classified as a 'toxic nephrosis', was well known as a complication of suicide attempts, accidental poisoning or attempts at procuring abortion. Occasionally, other poisons such as sodium chlorate, carbon tetrachloride or arsine gas were involved. The role of the uraemia in the deaths of the patients was not clear, however: most attention was paid to eliminating the mercury, and to achieve this intestinal lavage and sweating were used, which would also have helped the uraemia.

The revolutionary introduction of antimicrobial chemotherapy led to two new groups of patients with acute renal failure. The early sulphonamide drugs such as sulphadiazine, introduced in the late 1930s, were in general insoluble in urine, and high doses plus a lack of fluid (needed to allow the production of quantities of dilute urine) could induce *sulphonamide crystalluria*, from precipitation and blockage of the renal tubules as the urine was concentrated from the filtrate within the kidney.

Penicillin, introduced during the Second World War, allowed the survival of another group of patients—young women with infected, usually criminal, *abortions*, who survived their septicaemia (often the result of deadly organisms such as *Clostridia*) only to develop and often die of acute anuria. In Paris, these patients constituted as much as half the case-load just after the war [9] and emphasized the increased need for better management of the anurias. Such cases of abortion, however, although well recognized remained relatively uncommon in Anglo-Saxon countries.

Finally, one can make a good case that the *availability of new treatments* such as the various forms of dialysis and exchange transfusion in the 1940s focussed attention on this diverse group of patients, who were now identified as a group being suitable for such intervention, and led to the emergence of the global concept of 'acute renal failure' [10]. From 1946 onwards, this term was increasingly used. In 1953, in their paper called significantly 'The clinical course of acute renal failure'—an early use of this now popular term—Swan and Merrill [11] wrote:

> During the past 10 years a new concept of acute reversible renal failure has emerged. This concept has provided a common understanding of several previously apparently unrelated renal disorders.

As well as all the groups of acute renal failure just mentioned, Swan and Merrill dialysed a number of patients with anuria secondary to haemolysis from leakage of water (then used as irrigation fluid) into the circulation during prostatectomies—yet again an iatrogenic rather than 'natural' cause of acute renal failure.

We have seen that the publication of papers describing peritoneal dialysis led to widespread use of the technique in the late 1940s, especially in the United States, although usually only for single patients or handfuls of patients and during only a few years. The deceptive simplicity of the technique must have led many others, who did not publish, to attempt it and fail. There were still many difficulties: fluids had to be prepared, some sort of catheter selected and inserted, and a regime decided on, at a time when the literature gave little guidance as to how often or how long dialysis should be performed, or how the complications should be managed. Drainage of the fluid became difficult, the patients swelled up, their abdomens became infected. Soon, also, influential physicians were questioning the value of the technique.

Usable dialysis machines remained, in contrast, available in only a few centres. However, their availability did not lead to immediate acceptance of this treatment either [12]: on the contrary, in almost every country the same pattern of initial suspicion, scepticism and even antagonism was evident, and the introduction of haemodialysis as a routinely available treatment for acute renal failure was slow and erratic. This opposition had several strands: first of all, 'conservative management' had powerful advocates. This conservative management was not simply doing nothing, but involved careful limitation of fluid intake, and measures such as a high energy intake or anabolic steroids to limit the catabolism and rise in blood urea and potassium. As we shall see, influential individuals in several countries promoted this approach strongly (Fig. 10.2).

If one did favour active management, then equally there was a bewildering choice: exchange transfusion, and pleural, peritoneal and intestinal dialysis all had strong support at the time (see Chapter 9), and it is instructive to remember that in addition

(a)

(b)

(c)

Fig. 10.2 Three strong and influential advocates of 'conservative' management of acute renal failure, who opposed the introduction of dialysis as 'unnecessary': (a) Graham Bull (1918–1987) of the United Kingdom, (b) John P. Peters (1887–1956) of the United States, and (c) J.G.G. (Gerd) Borst (1902–1975) of the Netherlands (see text). ((a) courtesy Royal College of Phsyicians, London; (b) from [12]; (c) courtesy Dr Piet Borst.)

to studying and using haemodialysis, Kolff himself explored all of these techniques [13–15] as did many other contemporaries, including Alwall [16,17], and later Claus Brun and Jean Hamburger. There was no clear message as to what would prove be the best treatment in the long run, or whether there were any actually improved

outcomes in patients with acute renal failure. As late as 1950, even such a strong proponent and practitioner of dialysis, John Merrill himself, wrote [18]: 'it is not possible at the present time to draw definite conclusions as to the efficacy of such a procedure [haemodialysis] in the general treatment of renal disease'.

None of the procedures was easy to perform. A haemodialysis session was more of an adventure than a controlled form of treatment: Kolff's rotating drum dialyser, in particular, was clumsy, huge and so powerful it produced brutally rapid changes in the composition of the body fluids. Bleeding was common, rigors invariable. A sceptic witnessing such a chaotic séance was unlikely to be convinced. Finally, the attitude that the use of the artificial kidney was not 'science' was widespread (see below).

In contrast to the relatively encouraging results with peritoneal dialysis discussed in the previous chapter, during the early years of haemodialysis there were few cases where it could be said without equivocation that the intervention had saved lives, especially as the treatment was used almost always in those already moribund. There was, however, a plethora of patients with irreversible disease, on whose grim outlook dialysis had had little or no impact. Today, analysis of the literature published up to 1950 shows that haemodialysis had been used in 110 patients in 13 different centres in seven countries, of whom only 37 (34%) survived, even before bias in publication is taken into account. These results seemed a poor return to those such as Arthur Grollman, who despite his later experience as a pioneer of peritoneal dialysis (see Chapter 12) published a much-quoted paper in 1949 with his colleagues Eric Muirhead and J. Vanatta [19]. This reviewed their own and others' experiences with the use of the artificial kidney, including the most recent paper of Kolff [14] which reported six successes out of 16 patients. They emphasized yet again that acute renal failure was eventually a spontanously reversible condition, and that an effect of dialysis could not be discerned in most of the case histories published up to that time. They performed haemodialysis on nephrectomized dogs and failed to prolong their lives, despite the removal of urea [19]. They pointed out that many of the clinical effects of 'uraemia' could be attributed to disorders of sodium and water, brought about by well-intentioned but disastrous attempts to initiate a diuresis with large volumes of intravenous fluids, and could be cured by the correction of these using dialysis, not by removal of urea. In contrast, they reported that only four deaths had been observed in 27 consecutive cases of acute renal failure treated conservatively. They thus begin by advocating this course of management strongly. There arguments convinced many, and in several countries after initial enthusiasm for its use, dialysis languished for up to a decade.

In addition the kidney remained the first organ for which complete substitution (as opposed to assistance, as with the iron lung) had been proposed. There was also a deep suspicion of the idea that technology could replace a vital function, and this feeling was present in almost all medical circles. Even so, the public at large was fascinated, and articles appeared in the press in almost every country where haemodialysis was performed describing the new technique and lauding its (all too rare) successes.

Some time previously the American James Gamble (1883–1959) and others had shown that glucose could inhibit the catabolism of proteins, promoting the idea of oral or intravenous glucose loading for renal failure. Alwall wrote [16]:

> It was my impression that this negative attitude was at least partly due to a crisis between generations with old and new ideas. The occurrence of new methods for oral and intravenous nutrition was expected to solve the therapeutic problems, especially in acute renal insufficiency. The artificial kidney and other active techniques were considered not only strange and dangerous, but also unnecessary.

Moreover, the clinical complexities of the states leading to (and resulting from) acute renal failure were only appreciated gradually as experience accumulated. The need for management of the patient as a whole, and in particular the water and electrolyte problems, soon indicated that survival by dialysis, as well as the procedure itself, created as many problems as it might solve.

Problems of fluid and electrolyte management had been brought into focus by the work of James Gamble and Dan Darrow in the United States [20], René Mach and Jean Hamburger in Francophone countries, and Douglas Black and others in the United Kingdom. At the same time, it became much easier to manage such problems through the introduction of flame photometry into medicine just after the Second World War. Previously, the measurement of electrolytes was a slow and tedious business, and potassium was particularly difficult to assess. The principle of emission flame photometry had been established as practical as early as 1929 by Henrick Gunnar Lindgårdh (1888–1969) [21], but it took more than a decade of refinement to make the machines fully practical. As flame photometers became more available and easier to use [22], these measurements became easier and more rapid, and the management of patients much more simple. Indeed, it is difficult to see how acute dialysis could have continued had some technique of electrolyte analysis applicable to a clinical setting not become available. Kolff himself benefited from a close acquaintance with one of the pioneers in this field in Europe, Ruud Domingo [23], an agricultural chemist who had used the technique to assess saline contamination of soils in the Dutch polders. This meant that Kolff had access to flame photometry at a very early stage.

It is interesting also to examine the professional milieu within which dialysis was introduced into hospitals throughout the world. Two of the pioneers of the artificial kidney in the 1940s were physicians, but one, Murray, was a surgeon. During the early period of dialysis up to about 1960, surgeons, and particularly urologists, played a major role in the introduction of haemodialysis technology; to the point where in some countries, such as Italy and Japan, physicians appear to have played no role at all in the initial stages. In the United Kingdom and most other countries, both urologists and physicians were involved jointly; whilst in the United States only one university-based service, that in the Michael Reese Hospital in Chicago, had the artificial kidney unit sited within a urological service [24]. In addition, the majority of the early papers describing the use of peritoneal dialysis came from surgical and not medical units; surgeons in the United States strongly preferring this technique to what many of them perceived as over-complicated machines.

All this perhaps reflects the ancient attitude to surgeons as 'doers' and physicians as 'thinkers'. Dialysis came under the heading of 'active' treatment—indeed this phrase occurs in some papers of the period, as in the quotation from Alwall above. Gradually, however, the urological involvement became less, and fewer and fewer urologists were

seen at the meetings of those concerned with dialysis during the late 1950s and 1960s, and almost none beyond 1970. Harold McDonald of Downstate Medical Center, Brooklyn (1933–1991) (see Chapter 15) was one of the last pioneering urologists who worked in the dialysis field during the 1960s. The surgical/medical dialogue continued, of course, when peritoneal or blood access was under consideration, although in many units this was taken over by the physicians as well, who did no surgery other than access surgery, but became expert at it. This was true even after the arteriovenous fistula was introduced for long-term dialysis in 1965 (see Chapter 14). It has been remarked by many that nephrologists involved in dialysis tend to have the personality and skills of surgeons and not physicians, if such stereotyping is deemed to be possible. The final medical/surgical interface remained when patients on dialysis came up for transplantation. Initially the practice of transplantation was completely separate from dialysis in most centres—it is often forgotten that routine dialysis of uraemic patients before they were transplanted began only in the middle to late 1960s. Most early living donor and even cadaver grafts were done in undialysed, overloaded, anaemic, uraemic individuals whose massive post-transplant diuresis could—and sometimes did—kill them because neither the physicians nor the surgeons looking after the patients realized the basic importance of electrolyte balance.

Notes and references

1. Ratcliffe P. The pathophysiology of acute renal failure. In: Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls C, eds. *Oxford textbook of clinical nephrology*, 2nd edn. Oxford University Press, Oxford, 1998: 1531–56.
2. The oliguria following accidental or surgical trauma is more complex than just volume depletion, however; it occurs even in well-hydrated subjects after surgery, and results in addition from increased secretion of arginine vasopressin through non-osmotic triggers such as pain, and the opiates used to treat it, which in turn leads to volume-independent increased reabsorption of water in the kidney.
3. Prostration by the desalinating effects of cholera came to notice when cholera made its way to Europe in the 1820s and remained a feature of European medicine for the next century. In an epidemic of December 1831 in Scotland, suppression of urine in dehydrated cholera sufferers was noticed by a Dr Lawrie of Glasgow. The following year, the disease spread and many remedies were advocated, including the administration of saline fluids by Dr W.B. O'Shaughnessy of Sunderland in the *Lancet* (1831–1832; **i**: 490) who noted 'the blood … has lost a large proportion of its water … its neutral saline ingredients … [and] the free alkali'. Thomas Aitchison Latta (179?–1833), a young surgeon working in his home town of Leith, Edinburgh, also saw the high ratio of red blood cells to plasma when these unfortunate patients were, after the fashion of the time, bled to relieve their sufferings. In contrast, Latta adminstered large volumes of saline solution intravenously through a silver cannula using an enema syringe, warmed and filtered but unsterile, with relief of anuria in three of five initial patients so treated (see: Hoy C. *A beacon in our town. The story of Leith Hospital*. Edinburgh, 1988: 11–15; Latta T. Documents relative to the treatment of cholera by the copious injection of aqueous and saline fluids into the veins. *Lancet* 1832; **ii**: 274–7). Latta's work remained relatively unknown, perhaps because he was modest and died of consumption the following year. Similar observations and treatment were, however, made by F. Magendie in France (*Leçons sur le cholera morbus*. Collège de France, Paris, 1832: 116–50). These successes were only occasionally repeated for another century, however

(see, for example: Jackson TC. Report of a fatal case of cholera treated by the saline injection. *Lancet* 1849; **ii**: 144–5). For a history of intravenous fluid administration, see: Gamble JD. Early history of fluid replacement therapy. *Pediatrics* 1953; **11**: 554–67. For a consideration of surgical shock from blood loss, see: Moffat LE, Hamilton DN, Ledingham M. To stop his wounds, lest he do bleed to death. A history of surgical shock. *J R Coll Surg Edinb* 1985; **30**: 73–81.

4. Probably the earliest description of acute renal failure is that of Frankenthal L. Verschüttungen. *Virchows Archiv* 1916; **1916**: 222–32. The toxic agent was later demonstrated, after further papers by A. Hackradt (*Über akute tödliche vasomotorische Nephrosen nach Verschüttung*. Inaugural dissertation, München, 1917) and others, to be myoglobin by S. Minami (Ueber Nierenveränderungen nach Verschüttung. *Arch Pathol Anat* 1923; **245**: 247). For the early history of rhabdomyolysis, see: Better OS. History of the crush syndrome: from the earthquakes of Messina, Sicily to Spitak Armenia 1988. *Am J Nephrol* 1997; **17**: 392–4, and of acute renal failure in general, see: Brun C. *Acute anuria*. Munksgaard, Copenhagen, 1954; Chapter 1; and refs [5] and [11] below. No complete history of acute renal failure as a concept has yet been written.
5. Bywaters EG. 50 years on: the crush syndrome revisited. *Br Med J* 1990; **301**: 1412–15.
6. Lucké B. Lower nephron nephrosis. *Milit Surgeon* 1946; **99**: 371–96. This paper, published in what was then an obscure journal, was nevertheless of great influence and much cited. Jean Oliver famously commented of the title as 'euphonious, but erroneous'.
7. Only after about 1960 did blood typing and cross-matching become sufficiently accurate that such cases all but disappeared. Thus the era of acute renal failure arising from mismatched blood transfusion was short—from about 1930 to about 1960. For a history of blood transfusion, see: Diamond LK, A history of blood transfusion. In: Wintrobe MW, ed. *Blood pure and eloquent*. McGraw Hill, New York, 1980: 559–688.
8. A description of mercury poisoning causing anuria has been attributed to Ulrich von Hutton in 1519; see A Fishberg *Hypertension and nephritis* (1939 edn, pp. 305, 312), who quotes the thesis of a M. Roussel in Paris, 1911 (*La néphrite mercurielle*, p. 456).
9. Richet G. Les débuts de la dialyse à l'assistance publique de Paris. *Sem Hôp Paris* 1999; **75**: 162–4. The reasons for the lower incidence of acute renal failure from infected abortions in the United Kingdom and North America at this time is not clear, since the practice of illegal instrumental abortion was widespread.
10. The earliest paper I have traced using it is as early as 1928: Apert ME, Bach E. Insuffisance rénale aiguë chez un tuberculeux. Nécrobiose frappant toute l'étendue de la substance corticale des deux reins. *Mém Soc Méd Hôp Paris* 1928; **44**: 471–6. Other papers used various terminologies to describe the syndrome, from the 'vasomotor nephropathy' of Hackradt in 1917 to Lucké's 'lower nephron nephrosis' of 1946, which was most popular for 5–10 years after the Second World War; starting about 1945 'acute renal failure' or 'acute renal insufficiency' then became almost universal.
11. Swan RC, Merrill JP. The clinical course of acute renal failure. *Medicine (Baltimore)* 1953; **32**: 215–92.
12. Peitzman S. Origins and early reception of clinical dialysis. *Am J Nephrol* 1997; **17**: 299–303.
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15. Kolff WJ. Forced high calorie, low protein diet in the treatment of uremia. *Am J Med* 1952; **12**: 667–9.

16. Alwall N. On the organization of treatment with the artificial kidney and clinical nephrology in the 1940s and following decades. A contribution to the history of medicine. *Dial Transplant* Part I The nineteen forties. 1980; **9**: 307–11; Part II The turn of the decade 1949/1950 1980; **9**: 475–508; Part III The nineteen fifties 1980; **9**: 559–69; Part IV The nineteen sixties 1980; **9**: 669–713; Part V The nineteen seventies 1980; **9**: 752–7.
17. Alwall N. *Therapeutic and diagnostic problems in severe renal failure*. Munksgaard, Copenhagen, 1963.
18. Merrill JP, Smith S III, Callahan E, Thorn GW. The use of an artificial kidney. II Clinical experience. *J Clin Invest* 1950; **29**: 425–38. The results of this large series of cases—better than 50% survival—did much to turn the tide of opinion in favour of haemodialysis, after the rather dismal results in the preceding patients, summarized in the text.
19. Muirhead EE, Vanatta J, Grollman A. Acute renal insufficiency. A comparison of the use of an artificial kidney, peritoneal lavage and more conservative measures in its management. *Arch Intern Med* 1949; **83**: 528–31.
20. Holliday MA. Gamble and Darrow: pathfinders in body fluid physiology and fluid therapy for children, 1914–1964. *Pediatr Nephrol* 2000; **15**: 317–24.
21. Lundegardh H. Investigation of quantitative spectra analysis. II: Determination of potassium, magnesium and copper in flame spectrum. *Ark Kemi Min Geol* 1928; **10A** (1).
22. Hald P. The flame photometer for the measurement of sodium and potassium in biological fluids. *J Biol Chem* 1947; **167**: 499–510. See also: Epstein FH. John P. Peters and nephrology. *Am J Kidney Dis* 2001; 37: 113–9, in which the role of Phyllis Hald and John Peters in the introduction of the flame photometer into nephrology is discussed. Although Ruud Domingo's work in the Netherlands was done earlier than Hald's, it remained unknown in the United States and was not published until later (Domingo WR, Klijne W. A photoelectric flame photometer. Biochem J 1949; 45: 400).
23. Drukker W. Haemodialysis: a historical review. In: Maher JF, ed. *Replacement of renal function by dialysis*, 3rd edn. Kluwer, Dordrecht, 1989: 19–86.
24. Schreiner GE. Personal communication.

Chapter 11

The spread of dialysis technology for acute renal failure (1947–1960)

Given the background and initial scepticism about this novel form of treatment, what was the impact around the world from 1947 onwards, after the first pioneer descriptions of haemodialysis?

Europe

Even in the *Netherlands*, there was strong opposition to the use of the artificial kidney, although another Kolff kidney was used in Nijmegen in 1947 by Drs Enneking and Geelen [1]. This opposition was led by the influential Professor J.G.G. (Geed) Borst (1902–1975) of Amsterdam (see Fig. 10.2c) who advocated conservative dietary and electrolyte management of uraemia using 'Dutch gruel' [2] (water, custard powder, sugar and butter providing 1750 kcal daily with no nitrogen), and did not believe that lives could be saved by dialysis. Borst boasted that their artificial kidney—donated by Kolff—was rusting in the attic unused, because it was not needed [2]. Such was the opposition to his ideas in the Netherlands that in 1950 Kolff emigrated to Cleveland in the United States. Dialysis continued only in Rotterdam, where Kolff's pupil E.E. Twiss used an Alwall dialyser. Only in 1959 was dialysis re-introduced to Amsterdam by William Drukker.

Despite Alwall's meticulous studies, his unit in Lund remained for 13 years the only one in *Sweden* (Table 11.1); only in 1960, after a second unit had opened in Umeå in the remote north of the country in 1958, did the capital city of Stockholm start using haemodialysis [3]. During the 1950s, patients were said to have been 'Alwallized' if they received dialysis treatment, with the implication that this was a prelude to burial.

In *Great Britain*, Eric Bywaters (b. 1914) (Fig. 11.1a), who had described the crush syndrome in the London blitz of 1940 [4], and A. Mark (Jo) Joekes (b. 1922), a distant relative of Kolff's family, were working together at the Hammersmith Hospital in London in 1946. Bywaters went to Kampen to see Kolff as soon as the war was over, and with characteristic generosity Kolff came to London and gave them a rotating drum kidney. This was used from October 1946 to treat more than a dozen patients in London [5], amongst the first successful dialyses performed anywhere in the world and in time for an addendum in Kolff's *New ways of treating uraemia* of 1947 [1]. Although Bywaters and Joekes' paper is little cited today, in fact they dialysed their first patient only a month after Alwall's, and thus were the third group in the world to

Table 11.1 Early uses of haemodialysis in humans up to the end of 1949*

Investigator(s)	Date	Type of dialyser†	Place
1. Georg Haas	Feb. 1925	Collodion‡, own design	Giessen, Germany
2. Johan (Pim) Kolff	March 1943§	Rotating drum, own design	Kampen, the Netherlands
3. Rhoads & Saltonstall	Spring 1944¶	Static "coil", own design	Philadelphia, USA
4. Nils Alwall	June 1946	Static coil, own design	Lund, Sweden
5. Eric Bywaters & Mark Joekes	Sept 1946	Rotating drum (Kolff)	London, UK
6. Gordon Murray	Oct. 1946	Static coil, own design	Toronto, Canada
7. Michael Darmady	Early 1947	Rotating drum (modified Kolff)	Portsmouth, UK
8. Conrad Lam & Joseph Ponka	1947	Static coil (Murray)	Detroit, USA
9. Russell Palmer	Sept 1947	Rotating drum (Kolff)	Vancouver, Canada
10. Enneking & Geelen	Early 1947	Rotating drum (Kolff)	Nijmegen, the Netherlands
11. Maurice Dérot	1947	Formalinized intestine	Paris, France
12. Isidore Snapper	Jan. 1948	Rotating drum (Kolff)	New York, USA
13. Nannie de Leeuw	Feb. 1948	Rotating drum (Kolff)	Montreal, Canada
14. John Merrill & John Thorn	June 1948	Rotating drum (Kolff)	Boston, USA
15. Kurt Steinitz	1948	Static coil (Alwall)	Haifa, Israel
16. J. van Noordwijk & J.S. Brien	May 1949	Rotating drum (Kolff)	London, Ontario, Canada
17. Leonard Skeggs & Jack Leonards	May 1949	Flat plate, own design	Cleveland, USA
18. Tito de Ribeira	May 1949	Static coil (Murray)	Sao Paulo, Brazil
19. Bodo von Garrelts	Aug. 1949**	Static coil, own design	Stockholm, Sweden

Table 11.1 *contd.*

Investigator(s)	Date	Type of dialyser+	Place
20. Maurice Dérot	Oct. 1949	Rotating drum (Kolff)	Paris, France
21. Sterling & Doane	1949	Flat plate, own design	New York, USA
22. ?††	Oct. 1949	Allis–Chalmers (Kolff)	Milwaukee, USA
23. ?††	1949	Flat plate (Kolff)	Leiden, the Netherlands

* Undoubtedly this list is incomplete, as a number of early uses in the table were never published, and there are others which have yet to come to light. A number of Murray and Alwall kidneys were on site in other places in the late 1940s (see Chapter 8) but there is no record of their use. The same is true of the Kolff rotating drum kidney donated to Cracow, Poland. In a few other instances it is not clear whether dialysis may have started in 1949 or in 1950, as in the 'flat-coil' dialyser of Rosenak at the Mt Sinai Hospital in New York.

† Half of all the early dialyses following the pioneer efforts were done using some modification of Kolff's rotating drum design, despite its practical difficulties. However, the variety of approaches adopted is also impressive in these early years.

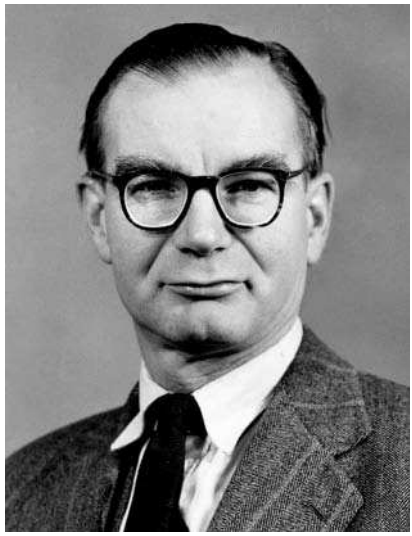
‡ All other models of dialyser listed here used cellophane membranes and heparin anticoagulation, with the sole exception of the use of prepared intestine in Paris.

§ First survivor, September 1945.

¶ Dr Rhoads also says in another account that it was in early 1945.

** Although von Garrelts first described his coil dialyser in 1947, the only paper on its clinical use I have been able to identify was published as late as 1956. In this, a patient treated in August 1949 is the only one of whom details are given—even the total number treated (probably quite small) remains obscure.

†† The name(s) of the urologist(s) concerned (do(es) not appear to have been recorded, only the personnel at Allis–Chalmers who created the machine (Jack Wilson and Walter Geist).



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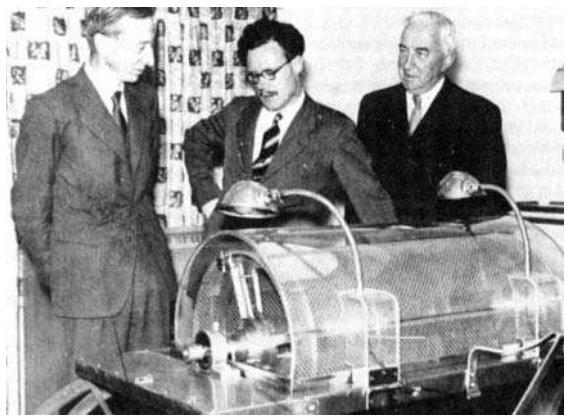


(c)

Fig. 11.1 (a) Eric Bywaters (b. 1913), who both described the crush syndrome in victims of the London Blitz of 1941 and thus focused attention on acute renal failure, and then performed some of the earliest dialyses to treat the condition in 1946–1947 using a Kolff rotating drum dialyser, together with (b) Mark (Jo) Joekes (b. 1921). When they stopped, dialysis was only re-introduced into the United Kingdom by (c) Frank Parsons (1925–1989) in 1956 who is seen in this well-known photograph trying to persuade Sir Harold Himsworth of the Medical Research Council (left) of the virtues of the Kolff–Brigham machine (see text). ((a, b) courtesy Dr Bywaters; (c) courtesy Dr Frank Parsons.)

use dialysis, since Murray's artifical kidney was not used on a patient until 6 December 1946 (Table 11.1). Notably, Bywaters and Joekes' series included the first use of the artificial kidney to treat poisoning with salicylate in man, as Abel and his colleagues had demonstrated in dogs 34 years previously, and George Schreiner (b. 1926) was to popularize during the 1950s [6]. Joekes also improved the design of Kolff's kidney by opening the venous return, so that a burette could be used to reduce the very high pressures within the closed circuit. However, 10 of their 12 patients died, and Bywaters moved on to rheumatology.

Thus from 1948 to 1956 no more dialyses were done in the United Kingdom, except for 19 patients treated in Portsmouth in 1947–1948 using a development of the Kolff kidney, self-constructed by a local garage for the physician-pathologist E. Michael Darmady (1906–1989) [7]. Darmady placed his machine in a van, and went from hospital to hospital dialysing the patients on site. Only two of the 19 survived, however, and a change to full-time pathology put an end to his project. Darmady also designed in 1948 a much more advanced type of artificial kidney involving a flat-plate design but using tubing for the dialysis [8], and had a flame photometer built to his own specification in 1948 (!). Darmady, although little known today, became internationally known during the 1950s because of his work using the nephron microdissection method of Jean Oliver, and later for morphological studies on the kidney in old age.

Why were both peritoneal and haemodialysis abandoned in the United Kingdom for a decade? Again, as in the Netherlands, successful opposition came from those advocating rigid control of fluid balance, dietary management and anabolic steroid treatment. This view was promoted strongly by the group led by Graham MacGregor Bull (1918–1987) (see Fig. 10.2a) who took over at the medical unit of the Hammersmith Hospital when Bywaters left, with Mark Joekes now converted to Bull's ideas of conservative treatment [9]. Bull's regime (based on peanut oil and sugar) was even less palatable than Borst's and had to be given through a nasogastric tube; but this style of management achieved more than 50% survival in acute renal failure, which impressed sceptics [10] despite the lack of comparability between the mixed patients dumped on to dialysis as a last resort, and the younger fitter patients, generally with reversible renal failure, who were treated conservatively. When considering evaluation of the results of early dialysis today, it must be remembered that the idea of prospective controlled trials with randomization of subjects to alternative treatments was only just beginning to enter medicine in the late 1940s, and had not yet been applied to any extent, and not at all to renal diseases [11].

Bull's and Borst's attitude to dialysis was not so bizarre as might appear today: in the 1940s and 1950s (as discussed in Chapter 10 and demonstrated in Table 9.2), many cases of acute renal failure were from poisonings, mismatched transfusions, abortions or trauma in fit, young, anabolic subjects. Such regimes had a good chance of tiding these patients over only a few days of oligoanuria. Only in May 1956 did Frank Parsons (1921–1989) re-introduce a Kolff–Brigham rotating drum dialyser (described below) into the Urological Department of Leeds following a visit to Merrill's unit in Boston [12]. This was followed shortly, in 1957, by the urologist Ralph Shackman using the Usifroid version (described below) of Kolff's machine from Paris at the Hammersmith Hospital in London; and Joekes, again together with

(Sir) Ralph Jackson of the Royal Air Force, using the new Kolff twin-coil dialyser. Even then there was opposition: Parsons was told by the head of the British Medical Research Council, Sir Harold Himsworth in 1956 [12]: 'Parsons, try it … but remember, the country is against you'.

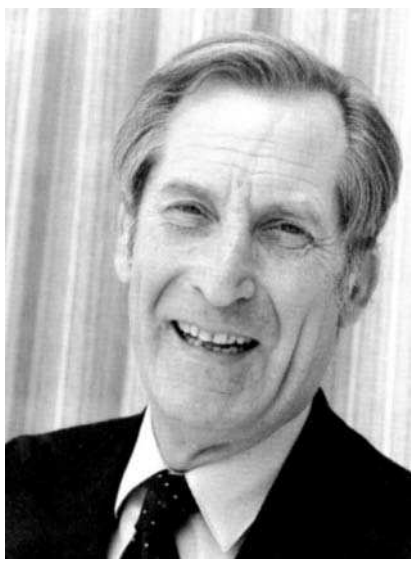
Nevertheless, by the end of the 1950s the need for regional dialysis units for acute renal failure was beginning to become recognized throughout the United Kingdom and units multiplied rapidly thereafter, starting in 1958 in Edinburgh, followed by Glasgow (twin coil), Newcastle (Alwall kidney), Belfast (twin coil) and the London Hospital (Kolff rotating drum), all in 1959. It is worth noting the role of surgeons in the re-introduction of dialysis into the United Kingdom: Parsons worked within a urology setting in Leeds as a member of a team headed by Pyrah; the Hammersmith unit was within the Department of Urology of Ralph Shackman; and the urologists accommodated and ran the unit in Belfast with help from a physician Mary (Mollie) McGeown. In other institutions (including Guy's Hospital where dialysis began in 1962) urologists and thoracic surgeons pressed for dialysis to be available for their postoperative patients with acute renal failure, now in increasing numbers with operations involving more prolonged cardiopulmonary bypass, such as aortic valve replacements, performed at pump perfusion rates which later turned out to be much too low.

In *France*, Maurice Dérot (1901–1985) (Fig. 11.2b) had a major interest in acute renal failure, and in 1947 treated an unfortunate patient who fatally ingested sodium chlorate by mistake, using an extracorporeal arteriovenous pumpless dialysis system, involving (in a look back to Love's work of 1920 [13]) a length of formalinized guinea-pig ileum in a bath of dialysate as an 'artificial kidney'. Two dialyses were performed, but were too short to have affected the outcome [14] although urea was shown to have been removed by the system. Dérot visited Kolff in 1948 to come away with plans for a rotating drum kidney. This, when built in Paris, began haemodialysis in France in 1949 at the Hôtel Dieu Hospital (Table 11.1), under the clinical supervision of Marcel Legrain (b. 1923) (Fig. 11.2a) [15,16]. His unit had been doing peritoneal dialysis, also under the direction of Pierre Tanret (1909–1965), since 1947 (see Chapter 10), and thus pioneered both techniques in France: Dérot's contribution to French and world nephrology has been underestimated [15]. Rapidly they achieved a large experience of acute renal failure, enhanced when Legrain spent time in Boston with Merrill in 1951.

Only later, in November 1954, did Jean Hamburger (1909–1992), Gabriel Richet (b. 1916) (Fig. 11.2c) and their colleagues at the Necker Hospital obtain a Kolff–Brigham kidney (see below) [17] after Richet had visited Merrill's unit in Boston. Prior to this, from 1948 onwards (as discussed in Chapter 10) they had used conservative management and intestinal dialysis with some success [18]. At this time Jean Dausset (1916–1998), as we have seen, was also treating acute anuria using exchange transfusion [19]. There had been laboratory trials at the Necker Hospital from 1952 with an Alwall kidney, but this impressed them so much with the difficulties of its use that it was never employed clinically. However, once started on haemodialysis the Necker team moved rapidly and accumulated experience quickly, thanks to their deep understanding of the intricacies of the uraemic state, and their

(a)

(b)



(c)

(d)

Fig. 11.2 Pioneers of haemodialysis in France: (a) Marcel Legrain (b. 1923), (b) Maurice Dérot (1901–1985), (c) Gabriel Richet (b. 1916), and (d) Jean Crosnier (b. 1922). To begin with the Necker Hospital group were skeptical of haemodialysis, but were converted by Merrill's success by the mid 1950s. (Courtesy of the subjects.)

agreement with Merrill's concept of total care of uraemic patients rather than just concentrating on the dialytic procedure itself [20,21]. Merrill himself had spent some time in Paris in 1956–1957 and, unusually for an American physician, spoke and read French. The Kolff–Brigham kidney was redesigned locally as the Usifroid version and, apart from its extensive use by the team headed by Jean Crosnier (b. 1922) (Fig. 11.2d) at the Necker [17,22], this was employed throughout France and exported to a number of other countries, including to the USSR. Again the emphasis at the Necker Hospital, as in the Hôtel Dieu and Boston, was on acute renal failure in all its aspects, and not merely dialysis using an artificial kidney.

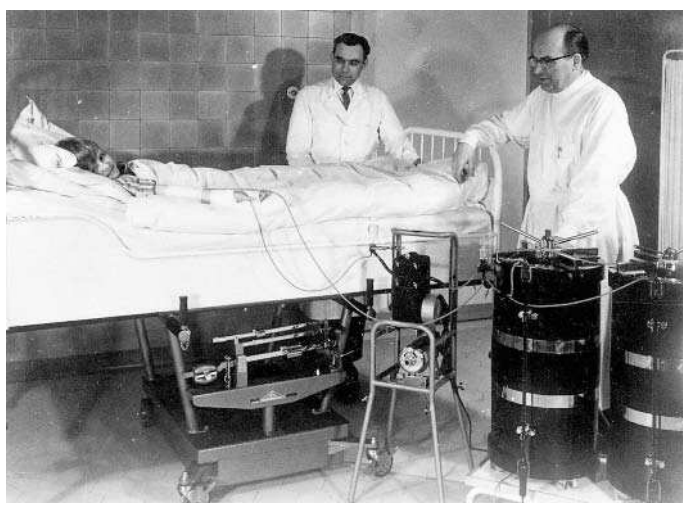
In *Germany*, despite the devastation of war, Franz Volhard heard of Alwall's work in 1947, and contacted him to ask if they could have an Alwall-type kidney [23], but Alwall unfortunately was unable to comply. This was discussed further in Munich in 1950 when Alwall visited to lecture, and a kidney was readied for shipment, but this was shortly before Volhard's death in a road accident so that in the end nothing came of it. This episode is interesting because of Volhard's attitude 20 years previously to Haas' experiments noted above. In the end a locally made Alwall-type artificial kidney was constructed and used first in December 1950 for acute renal failure by Curt Moeller (1910–1965) (Fig. 11.3) in Hamburg [24,25]. This model was quite widely used in Germany during the next 10 years [25]. Then came the work in Freiburg (see Chapter 8) in which the Nephra I flat-plate dialyser, based on the Murray–Roschlau kidney developed by Halstrup, was initially employed [26], followed by the more efficient Nephra II. By the late 1950s there were a number of centres in Germany using artificial kidneys, some of the Moeller–Alwall type, some twin coils. Germany was unusual in that rotating drum dialysers were never used, so far as I can establish.

Dialysis came late to *Spain*. During the 1950s, as Julio Botella has written [27]:

> Universities in Spain were still suffering the effects of the Spanish Civil War: there were almost no teachers or schools. Doctors could qualify and practice without ever having seen a single patient or even being able to take a blood pressure … hospitals were places of charity, where patients went to die.

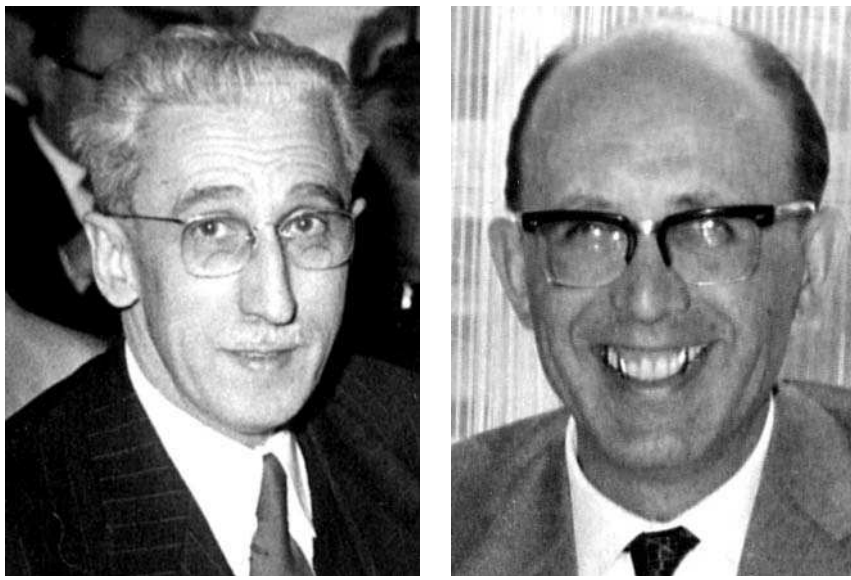
Not surprisingly, under these circumstances, the development of nephrology in Spain was delayed, although the Catalan urologist Luis Bartrina Soler (1903–1974) (Fig. 11.4a), working at the Hospital Clinic in Barcelona, noted the problems of Kolff's rotating drum dialyser discussed above and built, in 1949, a 'dialysis cell' into which the patient's blood could be drawn, dialysed then returned to the recipient—fractionated dialysis as perfomed by Haas, and initially by Kolff. The main advantage was that citrate anticoagulation of the blood in the cell could be used, without anticoagulating the patient. The disadvantage was low efficiency in removing solute. Initially, Bartrina experimented with cellulose tubes, but then evolved a flat-plate design of 'cell' which was immersed in the bath of dialsyate [28]. He treated 53 patients with acute, acute-on-chronic and chronic renal failure using this machine, but details of only a few are given, including the recovery of a patient with acute renal failure complicating pancreatitis, who was dialysed on three occasions and survived. This type of machine was used to start dialysis in *Hungary* also, where Nemeth, Pintér and Gäl in the University Department of Surgery in Szeged, and Mándi and Matolesi

(a)



(b)

Fig. 11.3 (a) Curt Moeller (1910–1965), a pioneer of dialysis in Germany who performed the first haemodialysis in that country on 17 December 1950, using a self-built version of the Alwall kidney (b). (Courtesy of Dr H-G. Sieberth, from [25].)



(a) (b)

Fig. 11.4 (a) Louis Bartrina Soler (1903–1974) of Barcelona, who built a 'dialysis cell' for fractionated dialysis in 1950, to avoid the problems of anticoagulation associated with Kolff's kidney (courtesy Dr Assunta Serra). (b) Emilio Rotellar (b. 1921) also of Barcelona, pioneer of haemodialysis in Spain, who introduced coil dialysis in 1957.

in Debrecen, again in a surgical department, performed the first dialyses in 1953 using modifications of Bartrina's dialyser [29].

However, dialysis in Spain really began long term in February 1957, when Emilio Rotellar (b. 1921) (Fig. 11.4b) started a haemodialysis unit in the Hospital Santa Cruz y San Pablo, again in Barcelona, using an artificial kidney modified from the Kolff design to minimize thrombosis [30–32], and a specially designed atraumatic blood pump. The following year acute dialysis began in Madrid at the Fundacion Jimenez Diaz under the direction of Dr Luis Hernando Avendaño, and the next year in Bilbao and the Canary islands.

Haemodialysis was a little slow to come into use in *Italy* also. There seems to have been almost no early use of either the Alwall or Kolff dialysers during the late 1940s, although Aminta Fieschi (1904–1991) of the Institute of Pathology in Siena had a version of the Kolff dialyser built in Milan in 1947 with some modifications, which he used clinically but abandoned because of the cardiovascular side effects [33]. When haemodialysis was finally introduced 6 years later in the early 1950s (peritoneal dialysis appears to have been very little used at all in Italy in this period [34]), it was using locally designed machines, almost exclusively built by general or cardiac surgeons and/or urologists; at that time physicians played no role in the introduction of dialysis, for reasons that are not clear. I have not been able to identify any focus of antipathy to the idea of dialysis in Italy as in some other countries discussed in this

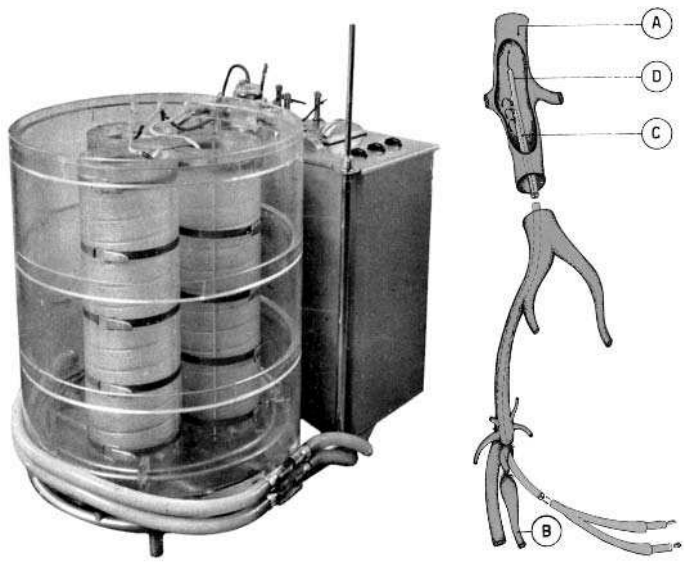
section. In contrast to (for example) the rest of Europe or even Latin America, there appears to have been little or no direct communication with those doing dialysis outside Italy, although the published papers in the early 1950s show that the world literature on the subject was well known to the Italian surgeons involved. They described their machines and published their results in Italian, and so their work was—and remains—little known outside Italy.

Several surgical groups began to use their own haemodialysis machines about the same time in 1952–1953. The first tentative clinical haemodialyses in Italy were done in 1953 by Mario Battezzati and Carlo Taddei of the University Department of Surgery in Genoa to treat three patients, one with acute renal failure [35]. They used a self-designed and built machine based on Taddei's previous experience of exsanguino transfusion which employed a number of dialysis tubes in parallel within a bath of dialysate. Another major force in the early years was Pietro Confortini (1924–1981) and his colleague Ferdinando Siracusano (b. 1925) in the University Department of Surgery in Padova [36], who first performed experimental dialysis in 1952, and then moved into humans using again the dialyser of Battezzati and Taddei, which they preferred to their own previous design. Confortini and Siracusano used a single-lumen venovenous central access with a blood pump, as Murray, and Battezzati and Taddei before them had done. Other surgeons involved with the design and use of haemodialysers in Italy were Franco Bianchi and Umberto Borghi in Modena, whose dialyser was an interesting design with a flat spiral of cellulose tubing in a closed container through which dialysate was pumped—rather like a two-dimensional coil kidney [37]. Also active were urologists Alberto Bonanome and R. Begani in Roma, and surgeons Mariano della Grazia and P. Torelli in Milano [38].

These early Italian experiences were gathered together and discussed at a meeting on haemodialysis held in Rapallo during 1–2 May 1954, one of the earliest meetings in nephrology and certainly the first on acute renal failure. It was confined to Italians, however, with the exception of Luis Bartrina Soler from Barcelona and Marcel Legrain from Paris [33].

Some of these pioneers formed the group with the greatest influence during the subsequent years of the decade, headed by the cardiovascular surgeon Professor Achille Dogliotti and his urological colleague L. Caporale in Torino, and Mario Battezzati of Parma together with Bianchi in Modena. Dogliotti was familiar with extracorporeal circuits, having been the first to use extracorporeal oxygenation in man in 1951 [39]. Although Caporale and colleagues had described a flat-plate design in 1954 [40], the new 1955 Dogliotti–Battezzati–Taddei artificial kidney was a triple-coil dialyser mounted in an open bath (Fig. 11.5), which was used in a number of units throughout Italy; a whole issue of the new journal *Minerva Nefrologica*—the first in the world to be devoted to nephrology—was given over to considerations of its use [41]. Interestingly in 1955 this machine was demonstrated by Confortini, and was then purchased and used by the local surgeon A.J. Leonsins for the first haemodialyses in Johannesburg, *South Africa* [42]. Perhaps because of Dogliotti's experience with extracorporeal circuits, a double-lumen central venous catheter was used for access along with the new machine (Fig. 11.5).

At last Italian physicians had become involved with the work of dialysis, in particular Antonio Vercellone (1923–2000) [43] who used this machine from 1956 in



(a) (b)

Fig. 11.5 (a) The Dogliotti–Battezzati–Taddei dialyser, used in a number of units in Italy throughout the late 1950s and early 1960s. (b) The double lumen venovenous access system. Dogliotti had considerable experience of extracorporeal circuits from his pioneering work with the cardiopulmonary bypass (see Chapter 2). (From *Minerva Nefrologica* [41].)

Torino [41]. Meanwhile, from May 1957, a Brigham–Kolff rotating drum dialyser was in use in Verona; a further Brigham–Kolff machine was sent to the University of Naples in 1960, which was one of the last to be exported from Boston [44]. From then on, use of the locally designed machines declined, and the twin-coil and other models became usual in Italy as elsewhere. Later, in 1964, long-term dialysis for chronic irreversible renal failure was begun in Italy by Confortini and his colleagues.

Latin America

In Latin America, as noted above, dialysis was started in 1949 in the Hospital das Clinicas, São Paulo, *Brazil* by Tito Ribeiro de Almeida (1913–1998) (Fig. 11.6) using a locally constructed kidney based on reading descriptions of Murray's Canadian design [45,46]. Probably he used Murray's design because it was so much easier to build than Kolff's. There were extensive trials in dogs to begin with, after which the first dialysis was performed on 19 May 1949 on a patient in chronic renal failure, but later that year an anuric patient with mercurial acute renal failure was successfully treated [47,48]. From then until 1954 over 100 patients were dialysed for acute renal failure, despite the rather poor performance of the design in removing urea. This represented the most extensive use of the Murray design anywhere, including Canada.

(a) (b)

Fig. 11.6 (a) Tito Ribiero de Almeida (1913–1998), pioneer of dialysis in Latin America who used a Murray-type kidney. The popular reception to the treatment is shown in (b), and was typical of the sudden public interest in renal failure brought about by the introduction of the new technology in almost every country. (From [47].)

A Kolff–Brigham kidney was then imported in 1955, a renal unit was set up under the Dr José de Barros Magaldi, and the Murray kidney was abandoned.

This illustrates the strong influence of the United States, both in training those who initiated dialysis units and in supplying the dialysers used in Latin America. In January 1955 another Kolff–Brigham kidney (see below) was in place in the J.C. Colimodio Hospital in Lagauaira, Venezuela, and yet and another was shipped to the Argentine Aeronautical Ministry in February 1955 [44].

However the first haemodialyses in *Venezuela* appear to have been done by Dr Alberto Guinand Baldó in 1958 after training in Boston. In *Argentina*, dialysis began in Buenos Aires in 1955, using a Kolff–Brigham-type kidney constructed locally by Alfonso Ruiz Guiñazú [49] at the University of Buenos Aires, followed shortly afterwards at the Centro de Educación Médica y Ivestigaciones Clinicas (CEMIC), using a Travenol twin-coil kidney. Two more Kolff–Brigham kidneys went to Rio de Janeiro and another to the Hospital das Clinicas in Sao Paulo (see above) in 1956, followed by two more to Uruguay in 1957 and another to Santiago de Chile in 1958, where D. Brailovsky carried out the first dialyses in that country. In Peru, the Whittembury brothers, Guillermo and José, doctor and engineer, designed and constructed a kidney based on the Kolff twin-coil design, and used it from 1957 onwards [50], followed by a Kolff kidney at the Hospital Obrero under the direction of Dr Alberto Piazza, which came into use later in that year. Thus by the end of the

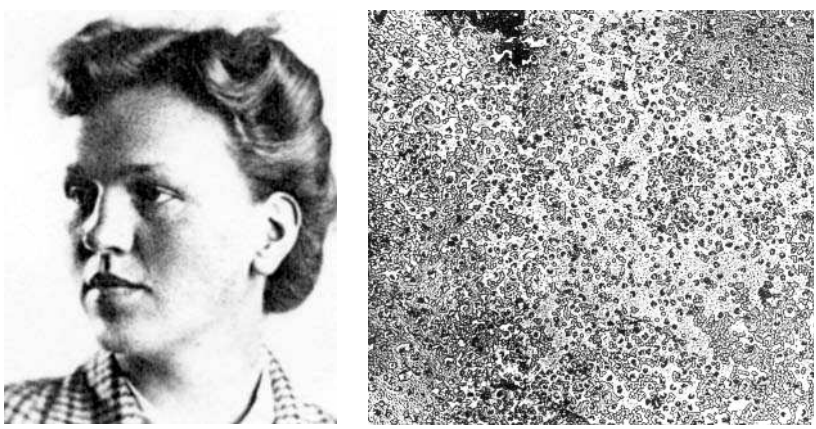
1950s, most countries in Latin America had at least one facility for dialysing patients in acute renal failure.

North America

Of the three countries in which dialysis was pioneered, only in *Canada* was there at least some immediate acceptance of dialysis. Apart from Murray's work in Toronto—which as we have seen was not well received locally—a rotating drum kidney donated by Kolff in 1948 was used [51,52] in the urology department of John T. Maclean in the Royal Victoria Hospital, Montreal by one of Kolff's ex-associates, Nannie de Leeuw (b. 1917) (Fig. 11.7a) who came to Canada in 1947. This work was notable for the first descriptions in 1949 of the early leukopenia during dialysis [52]:

> the white cells decrease in number at the beginning of the dialysis, but return to normal within a few hours. This is due to coating of the cellophane with leukocytes because of a positive chemotaxis.

In this paper, they cited work on cellophane-induced chemotaxis by Robert Chambers (the pioneer of micropuncture of cells) and C.G. Grand of New York University from 1936 [53]. In a detailed study of leukocytes in culture, Chambers and Grand noted and illustrated that whilst silk had no attractant effect, cellulose had a powerful chemotatic effect, with cells surrounding and adhering to the cellulose and dependent on a factor or factors present in serum. De Leeuw and Blaustein illustrated this part of their paper with a microphotograph of the exposed membrane (Fig. 11.7b), and



(a) (b)

Fig. 11.7 (a) Nannie KM de Leeuw (b. 1917) who began work with Kolff as a medical student, and started dialysis in Montreal in 1948 using one of his dialysers (courtesy Dr Jacob van Noordwijk). (b) Leukocytes adhering to the cellulose membrane of the dialyser, from the paper of Blaustein and de Leeuw in 1949 [52]—the first description of bioincompatibility. This observation was made also later in the 1950s, probably independently, in Japan (see text).

showed that *in vitro* sterilized cellophane would become coated with luekocytes but there was no drop in the total white count in the blood in which it was suspended. This showed that their explanation was correct only in part, perhaps because much of their work as done *in vitro* without the patient in the circuit, and their work was forgotten; 20 years later Goffinet and his colleagues rediscovered the phenomenon and gave a more complete explanation (see Chapter 17). Nevertheless, their idea that the cellulose in the artificial kidney caused the release of chemotactic substances was the first prescient description of bioincompatibility in dialysis, by almost 20 years.

Another rotating drum kidney was constructed from Kolff's plans after a meeting between Russell Palmer (1905–2000) and Kolff in Nijmegen in 1945 [54] and was first used in the Shaughnessy Hospital, Vancouver on 22 September 1947 [55]. Yet another was constructed in London, Ontario by another of Kolff's associates, Jacob van Noordwijk which was used clinically in 1949. This illustrates a major factor in the spread of haemodialysis: Kolff's generosity in constructing and donating kidneys not only to London and Montreal, but also to Cracow in Poland (where it was probably never used after it arrived in 1950) [3], New York and Boston (through which in modified form it circulated to many other sites, including Paris, and from there again as the Usifroid modification to several other countries, including the USSR).

The *United States* was, surprisingly, not one of the countries in which dialysis was pioneered. However, there was one attempt by Jonathon Rhoads in Philadelphia in 1944, whom we have met already for his work on peritoneal dialysis in the 1930s. In the discussion of a paper by Jacob Fine and his colleagues at the meeting of the American Surgical Society at Hot Springs, Virginia on 2–4 April 1946 [56], Rhoads commented in discussion, after briefly noting Abel, Ganter and Haas' work on dialysis,

> It is now easier to employ the method of Abel, Rowntree and Turner, because suitable tubes for dialysis can be obtained in the form of sausage casing, which is available in lengths of 100 feet [30.4 m]. About two years ago [i.e. spring 1944] Dr Henry Saltonstall and I set up a system of 60 feet [18.3 m] of this tubing in a bath of Ringer's solution with sufficient gelatin to counteract the osmotic pressure of the plasma proteins, and by heparinising the patient it was possible to allow his blood to flow out from an artery through this system and to reënter the circulation through the veins. This method, too, will reduce the urea nitrogen.

The patient was a young woman with post-partum acute renal and hepatic failure, the arteriovenous circuit was used without a pump and the tubing was wound on a test tube rack in the dialysate bath. The patient bled the evening after the procedure, probably because of the heparinization and liver failure, and died despite transfusion. This hitherto undiscussed attempt to make and use an artificial kidney in the United States early in 1945 [56] illustrates the fact that the idea of using cellulose tubing and heparin to do extracorporeal dialysis was widespread during the war years. Rhoads had not heard of Kolff's work, which came to attention in America only through the publication of his thesis in Dutch in January 1946, which Isidore Snapper of New York (himself a Dutch émigré) translated and circulated, and was mentioned in this discussion in April 1946. After the war Rhoads met Kolff when the latter visited the University of Pennsylvania. He had used approximately the same length of tubing as

Rhoads and Saltonstall, but how their dialysate was mixed or circulated is not recorded. Then there was the attempt at dialysis in two patients by Conrad Lam and Joseph Ponka using their self-built Murray-type static-coil kidney in Detroit in 1947, discussed further in Chapter 9 [57].

Despite the fact that the technology was imported to begin with, almost uniquely haemodialysis was accepted much more readily and promptly in the United States during the 1950s, with such effect that there were more than 110 units capable of performing the technique as early as 1959, and over 250 by 1962 [44]. This was the result of factors particular to the States. The first factor was that very early on Kolff donated one of his rotating drum dialysers to a fellow Dutchman from Amsterdam, Isidore Snapper, who after fleeing the Nazis in 1938 was now Professor of Medicine in the Mt Sinai Hospital in New York. There, Al Fishman and his colleagues Irving Kroop, Evans Leiter and Abraham Hyman performed the first really successful dialyses in the United States beginning on 26 January 1948 (Fig. 11.8) [58]; a further five patients were treated, four of whom died, however.

George Thorn (b. 1906) (Fig. 11.9a, left) had a major influence on the introduction of both dialysis and transplantation in the United States [59]. Primarily an endocrinologist, he had become interested in renal failure during the early 1940s, and with Charles Hufnagel and David Hume had used a temporary external kidney transplant attached to arm vessels to treat acute renal failure in 1947 [59]. At Thorn's request, Kolff visited the Peter Bent Brigham Hospital, Boston in 1947, and a year later John

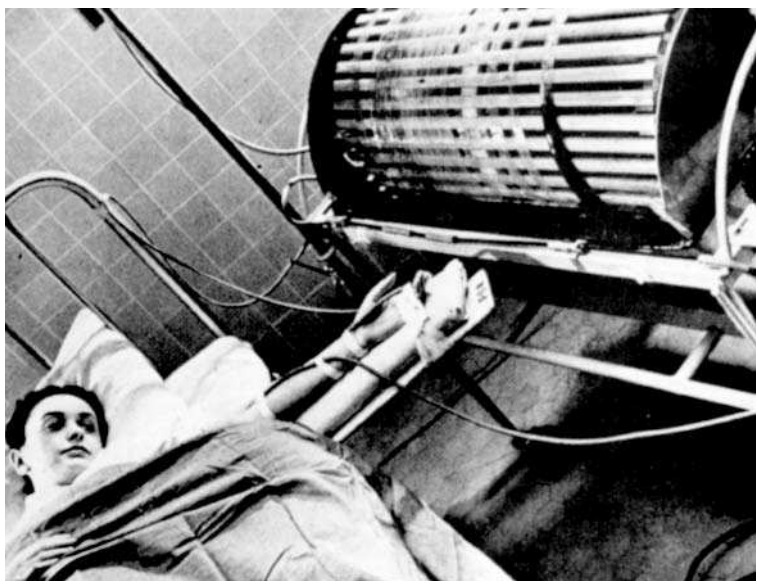
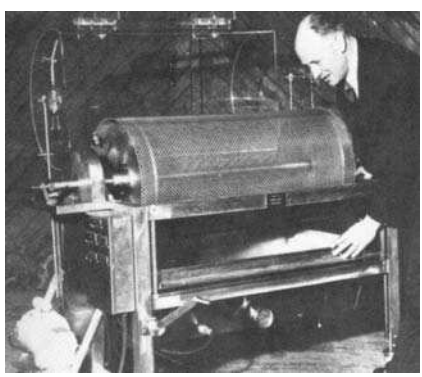


Fig. 11.8 Early dialysis in the Mt Sinai Hospital, New York, January 1948 using an artificial kidney donated by Kolff. This, together with the work in Boston beginning 6 months later, was the first effective use of the artificial kidney in the the United States. (Courtesy Dr Irving Kroop, from [44].)

Putnam Merrill (1917–1986) (Fig. 11.10), a Bostonian of patrician New England descent and a resident in the division of medicine working on electrolytes in cardiology [60], was put in charge of a renal failure programme, initially using another dialyser donated by Kolff. Their first dialysis was done on 11 June 1948 [61]. Then, from drawings supplied by Kolff, Brigham surgeon Carl Walter (1905–1992) (Fig. 11.9a, right) set out to modify and improve the kidney, initially at his own expense[62]. He had experience of plastics as a pioneer of blood transfusion technology, and had founded Fenwall Laboratories to promote this work. He employed an engineer, Edward Olsen (Fig. 11.9b), who led the work to redesign and rebuild the kidney into the Kolff–Brigham kidney (Fig. 11.11). This was manufactured in quantity, and was the standard form of artificial kidney in most units in the United States throughout the 1950s, as well as being exported to a number of countries abroad (listed in [44]).

Merrill played a major role in introducing dialysis in the United States. He set up a busy programme of dialysis, and had treated over 100 patients in acute renal failure within 3 years [63]. Not only did Merrill have access to technical expertise, but his team also had the clinical wisdom and knowledge to tackle the many electrolyte and other problems of acute renal failure. The Boston group were the first really effective all-round team to operate an artificial kidney, matched in the late 1940s only by the team at the Hôtel Dieu in Paris headed by Dérot and Legrain, who had a similar large

(a)



(b)

Fig. 11.9 (a) George Thorn (b. 1906) (left) and Carl Walter (1905–1992) (right); (b) Edward Olson. The physician Thorn was responsible for interest in haemodialysis in Boston, whilst surgeon Carl Walter employed engineer Olsen in his Fenwall Laboratory to improve and modify Kolff's dialyser. Thorn appointed resident John Merrill to head up the clinical team. (Courtesy Harvard Medical Library in the Countway Library.)

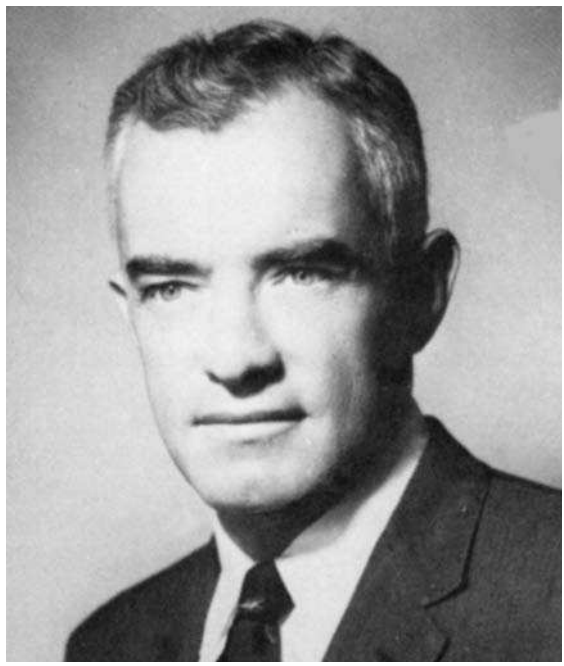


Fig. 11.10 John Merrill (1917–1986). Merrill was chief of the first group in North America with a major commitment to understanding all the metabolic problems of acute uraemia and acquiring the skills to manage them successfully. Merrill's influence on the treatment of acute renal failure was enormous, both in the United States and throughout Latin America and Europe. (Courtesy Harvard Medical Library in the Countway Library.)

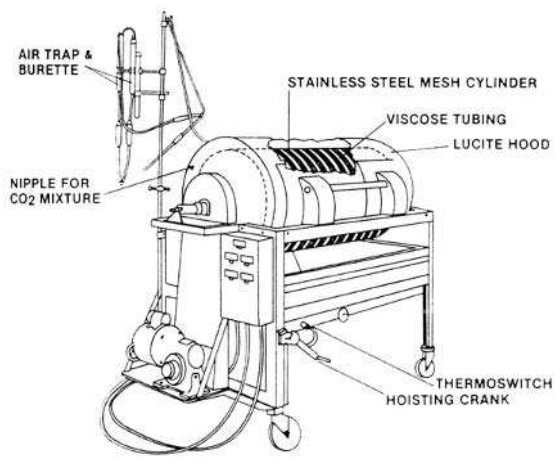


Fig. 11.11 The Brigham–Kolff dialyser, designed and constructed in Boston, was the standard dialyser throughout the 1950s until superseded by the twin-coil dialyser and later the flat-bed dialysers in the 1960s. (From [44].)

team and considerable experience of large numbers of patients [14,15] and with whom they were in close contact. In this context the group at Georgetown, Washington, who performed dialysis from 1950, must be mentioned also, and the somewhat later development of the Necker haemodialysis group has been discussed above. All these teams realized that dialysis was only a part of the total management of the oligoanuric patient, and that a profound knowledge of electrolyte physiology and balance was necessary, as well as attention to nutrition and microbiology. In contrast, in many centres throughout the United States and the rest of the world, dialysis machines were bought or constructed, then hauled out of storage occasionally and used as a desperate measure to treat patients dying of uraemia, without clear notions of clinical goals or details of general management; many machines simply rusted in idleness—perhaps to the benefit of the patients! These incomplete and premature essays in the use of haemodialysis did much to harm its image during the 1950s and to slow the useful expansion of the technology.

The second factor promoting acceptance of the artificial kidney in the United States was that Kolff, after several visits sponsored initially by Snapper in 1948–1949, accepted an invitation from Irvine Page to go and work long term in Cleveland, Ohio to where he moved in 1950. Page's idea was that Kolff should work on the role of the kidney in hypertension, not on renal failure or dialysis *per se*, far less the artificial heart which now preoccupied Kolff's thoughts. Kolff's presence in the United States was powerful advocacy for dialysis; he also—despite Page's relative indifference to this work—introduced technical advances to make it more available, in particular the design of the disposable twin-coil dialyser (see Chapter 12).

Nevertheless, opposition remained strong for a considerable period in the United States [64] and, as in the Netherlands and the United Kingdom, a single influential individual was crucial, in this case John Punnet Peters (1887–1956) of Yale. He had trained many of the physicians who were then in the process of becoming the first nephrologists in the United States. In addition, some of those initially convinced of the use of dialysis became sceptical—for example Al Fishman, who came to advocate conservative management in the late 1940s—and joined forces with the influential seniors, Peters [65] and Arthur Grollman [66]. Even in 1951, Lou Welt and Peters could write [65], echoing Merrill's cautious conclusions already quoted in Chapter 10 [67],

> the value and proper role of the variety of artificial dialyzing procedures remain a subject for investigation … it is not certain however that the use of this instrument has materially altered the ultimate fate of a patient ill with lower nephron nephrosis.

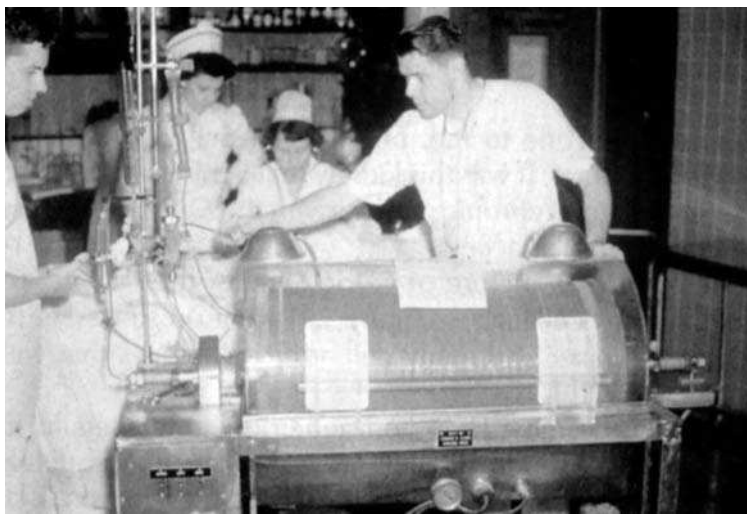
Richet [68] notes that when he visited Boston as late as 1954,

> I was surprised in noting that John [Merrill] was considered as an outlaw by the hospital staff and the members of the 'salt and water club'. They denied him any contribution, even the usefulness of the artifical kidney [regarded as] useless in New York, and his first attempts at renal transplantation.

But a major and unexpected motor of change appeared. In June 1950 North Korean troops crossed the 38th parallel and invaded South Korea. The United States and other Western powers were rapidly involved in the war, and US troops were in the

battlefield by July. Yet again, armed conflict resulted in major injuries to young men, some of them went into renal failure just as they had done in the Second World War and previous wars. On this occasion, however, the problem was immediately evident rather than retrospectively analysed: fighting began and casualties perished, some anuric early after trauma. As before, the mortality amongst those anuric was 85% (47/55 in a series analysed later by the US army surgical research team) rather than the general 5% of all battle casualties [69].

Dr Paul Doolan had moved from Boston to work in the Navy in association with Georgetown University, Washington, where one of the first Kolff–Brigham dialysers



(a)

(b)

Fig. 11.12 (a) George Schreiner (b. 1926) who played a major role in the introduction of clinical dialysis for acute renal failure in the 1950s is seen here in Georgetown, where dialysis was started in 1950 by Paul Doolan. Later Schreiner helped introduce long-term dialysis for chronic renal failure in the 1960s and in the early 1970s he undertook many of the negotiations to help expand the provision of dialysis in the United States. (From [75].) (b) Dr Schreiner today.

was installed and used in 1950. Doolan was consulted and under the direction of the Surgeon-General and the commandant of the Walter Reed Army Research Insitute, Colonel W. Stone, who sent an army taskforce to Korea to investigate death amongst battle casualties. Amongst this taskforce was one of Doolan's associates, George Schreiner (b. 1926) (Fig. 11.12) as physiologist/internist. This taskforce pointed out the risks of hyperkalaemia in oliguric patients following the new procedure of blood transfusion using stored refrigerated blood, and strongly recommended that haemodialysis should be available locally.

The US army had already set up an artificial kidney unit at Walter Reed Hospital in 1951 and in April 1952 this unit was moved to the 11th evacuation hospital near Pusan to receive casualties by helicopter, 30 minutes' flight from the forward MASH units; by this time, the battle line was stabilized some way to the north. The unit was initially under the direction of Lloyd H. (Holly) Smith and in June 1952 Colonel Paul Teschan (b. 1923) (Fig. 11.13) (both of whom had trained at the Brigham Hospital in 1950) took over as head of the dialysis unit, which was integrated within the surgical research team; he ran it until March 1953. More than 50 patients were dialysed, and the overall mortality fell to an impressive 38% [70–72]. From 1953 it came under the direction of Bill Mulroney.

Thus by 1956, although still reviewing all the alternative methods available, Merrill [73] could now point to the fact that haemodialysis was clearly effective in saving lives. George Schreiner has captured vividly the excitement of this period of transition, in which he played a major role [74,75].

Fig. 11.13 The use of the Kolff–Brigham dialyser in the 11th field hospital in Korea. Dr Paul Teschan, chief of the unit, is on the right. The success of the teams in Korea in reducing mortality from anuria was a major factor in convincing physicians in the United States of the utility of dialysis. (Courtesy Dr Paul Teschan, from [44.])

It is worth noting also the immediate interest of the technologically minded Americans in designing and improving dialysers as soon as the Kolff design became known: already by 1950 no less than six different new dialyser designs had been constructed in the United States alone—and most used clinically—besides the Kolff–Brigham version (see Chapter 12) [3,44]. However, most of the creators of these machines were not backed by clinicians with a full appreciation of how much more difficult it was to manage acute uraemia than it was to design and build an effective dialyser capable of removing urea and other solutes out of the blood.

It is also worth noting the beginnings here of the injurious divide between 'tradesman' dialysis physicians on the one hand, and 'physician-scientists' epitomized by Peters on the other, which has marred the development of nephrology in a number of countries, but particularly Germany and the United States. For the great majority of physician-scientists, dialysis simply was not science, but 'tinkering in basements'; matters were not helped that in the 1950s many hospitals' dialysis programmes worldwide were directed by urologists, so that it became regarded by physicians as 'just another technique', with no scientific content. Only gradually did dialysis become accepted as part of internal medicine. Peters', and Homer Smith's, trainees almost all followed their lead in not becoming involved with dialysis; a notable exception was George Schreiner. It is understandable that in the 1950s the many scientific questions of great interest and importance that would arise from the treatment of patients in renal failure were not yet evident—although work on the pathogenesis of hypertension in anuric patients was underway by the mid 1950s by Page and Kolff [76], and journals such as *Science*, the *Journal of Clinical Investigation* and the *New England Journal of Medicine* all published papers from the pioneers of dialysis in the 1940s and early 1950s.

Japan

In *Japan* dialysis began with the construction of both a tube dialyser based on the Abel design and also a flat-plate model by Kishio Shibusawa and Junpei Tang, initially in 1952 within the surgical department of Seiji Kimoto in the University of Tokyo. The latter model was used in Gunma University, Maebashi from 1954 in several hundred patients [77,78]. They and Nosé's group in Hokkaido [79] noted leukopenia during dialysis, as the Canadians had done earlier. In addition, a Brigham–Kolff dialyser was imported to Tokyo University in 1955 [3]. A number of other models of dialyser were constructed locally and used [80–84] including a further design from Seiji Kimoto in Tokyo, whose model was used elsewhere in Japan [81]. Other designs followed, some of them quite original, such as the kidney incorporating a dog lung, again by Kimoto and colleagues, reported in 1959 to the ASAIO [82]; and the tiny electrodialysis system of Takeshi Minami of Jikeikai University in Tokyo, used by Tsunetaka Kushimoto [83] and Nobuo Miki [84]. It is worth noting that all of these early developments, as in Italy, took place in departments of surgery and not of medicine.

Peritoneal dialysis in the 1950s

In contrast to the steady expansion in the use of haemodialysis for acute renal failure during the 1950s, especially in the United States, relatively little happened in the area

of peritoneal dialysis during this decade, until major advances were made in 1959 which were to bring it centre stage during the next decade. In the period from 1950 to 1955 only a handful of papers were published, and interest seems to have been low in the technique, although its simplicity allowed use in countries such as Turkey and Serbia, as well as reports from Germany, Switzerland and Norway. The main users of the technique in Europe continued to be Dérot, Tanret, Legrain and their colleagues in Paris [85,86], who were able to report on more than 200 patients treated in this way in 1951. Two years later, after he had spent a period in Boston, Marcel Legrain together with John Merrill reported a simplified intermittent dialysis [87]. The technique was then used in Boston throughout the 1950s for acute renal failure, with more than 200 patients treated by 1961. Waugh also published an important paper using a simple technique shortly afterwards [88].

In important and influential work, further careful studies of the kinetics of peritoneal dialysis in dogs were done by Arthur Grollman (1901–1977) (Fig. 11.14), working in the South Western Medical School in Dallas, Texas. Grollman was yet another from the prolific Johns Hopkins school, graduating in 1930 and working in the physiology and pharmacology units there with Abel, Eli Marshall and others. After a brief experience at the Bowman Gray Medical School during the Second World War, he moved to the South Western Medical School in Dallas in 1944. Although his main interests were in the endocrinology of cardiovascular physiology and medicine, particularly the adrenal hormomes, he had an enduring interest in ultrafiltration (see Chapter 17) and osmosis, and published first on acute renal failure (as we have seen earlier in this chapter) as a critic of the use of dialysis, in a powerfully argued and influential article.

Nevertheless, he became interested in the effects of the kidney in the control of blood pressure, and bilateral nephrectomy was an obvious starting point. However, this required in turn some means of maintaining the experimental animals without kidneys, and he turned to peritoneal dialysis. Thus his interest in the technique was oblique to the treatment of uraemia. His paper and short monograph on peritoneal dialysis published in 1951 [89,90] had a major and enduring influence on thinking in the field. The principles enunciated in his work were applied to human dialyses, including the idea of dwell time for the fluid within the abdomen and intermittent use of treatment, and became standard. Grollman also (and independently from Dérot) recommended the use of a flexible polyethylene catheter [91]. His son recalls [92]:

> when he [Grollman] was invited to speak at another hospital center, he would take along a small screw capped bottle containing ethanol and a polyethylene tubing which he punctured with a hot wire. He would put the bottle into his suitcase explaining that when he lectured in a hospital center on hypertension, he would invariably be informed that a patient was dying of renal failure and that hemodialysis … was not an option. After his lecture, Dad would visit the patient, ask for a standard abdominal trocar and a few bottles of lavaging fluid, insert the catheter and demonstrate how the dialysis was done. The procedure was simple and effective so he generally left immediately to catch his plane while the local staff carried on.

Despite this interest, from 1956 to 1959 only a further handful of papers appeared [93] and peritoneal dialysis as a technique seemed to have waned, just as the availability of haemodialysis expanded.

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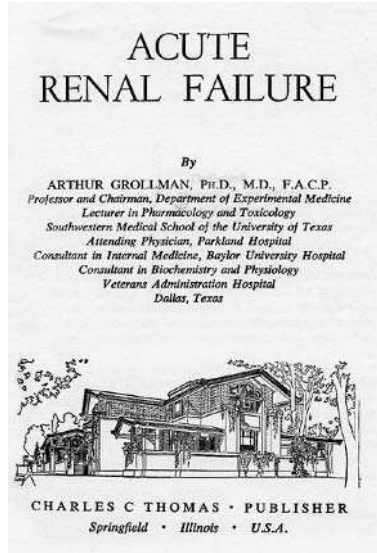

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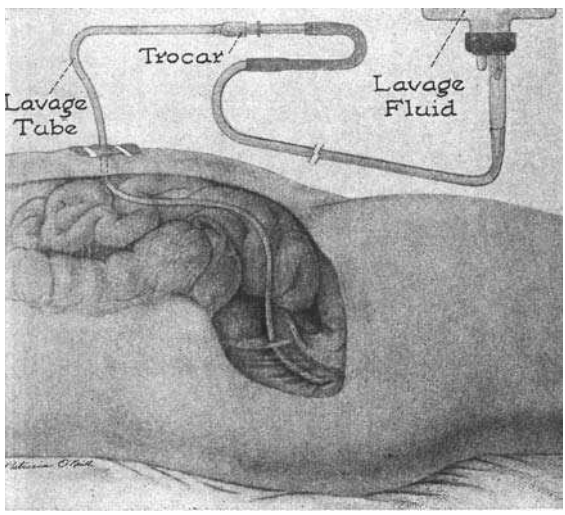


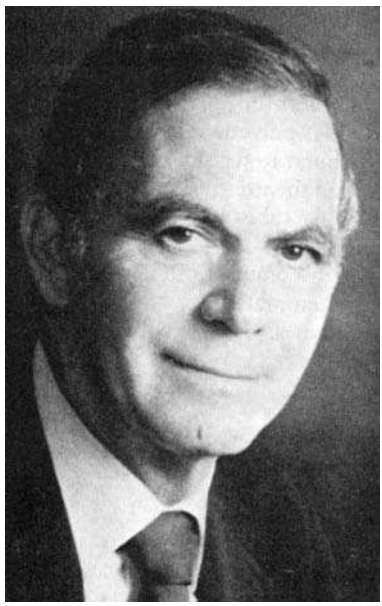
(c)

Fig. 11.14 (a) Arthur Grollman (1901–1977) whose influence on the management of acute renal failure, and in particular peritoneal dialysis, was considerable during the 1950s (courtesy Professor A. Pat Grollman). (b) The title page of Grollman's 1951 monograph. (c) The system used by Grollman. The flexible multihole polyethylene catheter made by hand became the prototype for the catheters used for the next decade, to be replaced by more rigid nylon catheters and silastic during the 1960s.

Then in 1959, progress was made quite suddenly. Grollman's description of dialysis was adopted in detail by Mort Maxwell (1924–2000) (Fig. 11.15a) in Los Angeles from 1956 onwards, to achieve by the end of the decade simple, readily available dialysis [94]. Maxwell had trained with Homer Smith, and then stayed at Bellevue Hospital in New York before going to California. There, he and his colleagues, seeking a simpler method of dialysis that could be more generally available than haemodialysis, persuaded the Baxter Corporation to manufacture 1 L glass bottles of dialysate of a composition based on Grollman's which became more or less standard, with (in retrospect) a rather too high sodium concentration of 140 mmol/L, and a high concentration of lactate (45 mmol/L) to avoid the problems of bicarbonate as a buffer. This had plagued previous attempts to produce a stable prepared solution since if calcium was also added, precipitation of calcium carbonate occurred. Maxwell's solution thus could contain 2 mmol/L of calcium; 15 g/L of dextrose monohydrate was added to prevent fluid absorption into the peritoneum and if ultrafiltration was required, then a stronger glucose solution was needed—usually 65 g/L. These 1 L glass bottles were easier to handle than the large carboys then in use, and were hung in pairs above the bed for drainage in, and then transferred to the floor for drainage out (Fig. 11.15b). Usually 10–20 minutes sufficed for inflow, and a dwell period then followed of 0.5–1 hours, followed by drainage. An additional advance was that a disposable set of Y-tubing made from polyvinyl chloride (PVC) (see Chapter 12) was available, with sharpened ends to insert into the bottles. This system had many advantages, and rapidly became popular as peritoneal dialysis could now be run as a nursing procedure after insertion of the catheter. Its main disadvantage, however, was that disconnection, with its attendant risk of contamination and infection, was necessary for every 2 L exchange. Exchanges of 2 L were recommended through a narrow, rather rigid, nylon multihole catheter, again made available commercially at Maxwell's instigation (from Cutter Laboratories), which could be inserted into an iliac fossa through any trocar, and tied into place. Other manufacturers (e.g. Abbott Laboratories, and in the United Kingdom Allen and Hanbury's) started selling bottles of prepared dialysate. Thus peritoneal dialysis had become standardized and relatively easy to perform.

Problems still remained with the catheter access, however. Also in 1959 Paul Doolan (b. 1924) (Fig. 11.16a) and his colleague William Murphy (who had previously worked with Merrill) at the US navy hospital in Oakland, California described an improved catheter [95], again with multiple side holes, but made of soft PVC, with ridges ringing it to prevent blockage of the drainage holes. It required a larger trocar (24 Fr rather than 17 Fr for the Maxwell catheter) to insert, or even a small surgical laparotomy, and thus it was not widely used. However, the use of the new soft plastics was an important predictor of what was to come in the1960s. Doolan's group also used disposable materials and bottles of dialysate, containing a much lower sodium concentration than Maxwell's (128 mmol/L). They returned to using bicarbonate as buffer, which meant they had to inject any calcium required into a peripheral vein.

Finally, in the same year of 1959, a thesis was published by a young Dutchman, 'Fred' Boen (b. 1927) [96] who was then working in J.G.G. Borst's unit in Amsterdam [97]. This described kinetic studies of peritoneal transfer which had been done from



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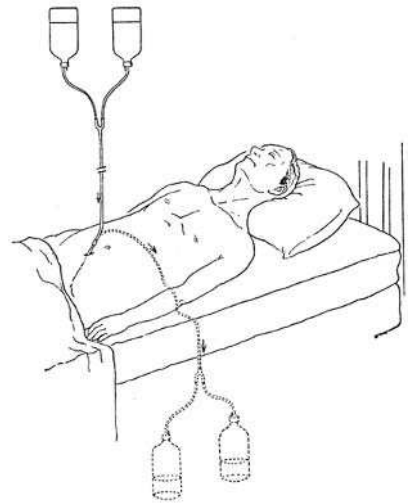

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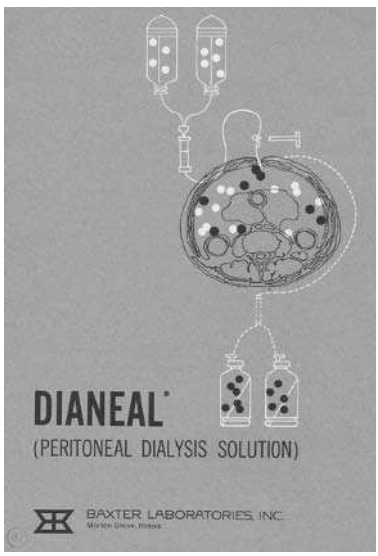

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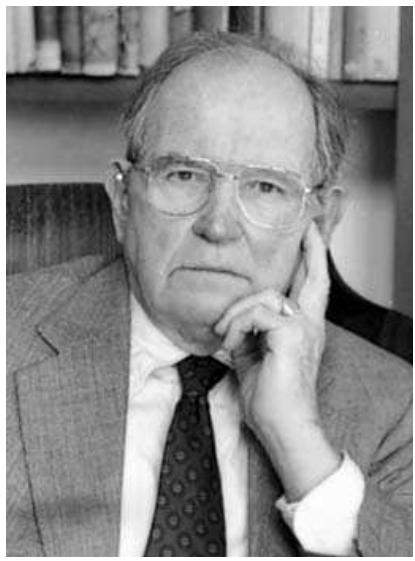
Fig. 11.15 (a) Mort Maxwell (1924–2000), whose simple commercially available dialysis set and catheter became the standard for the 1960s. (b) The 'twin bottle' peritoneal dialysis system of Maxwell (from [94] with permission). (c) The first commercially available fluid and giving set for peritoneal dialysis.

1957 onwards, which amplified those of Fine [98], Grollman [89,90] and others previously. It was published as a monograph in the United States, and commanded wide attention, including from Belding Scribner in Seattle. Boen had been born in Jakarta, Indonesia, and after qualification there came to Amsterdam in 1949, and was to play a



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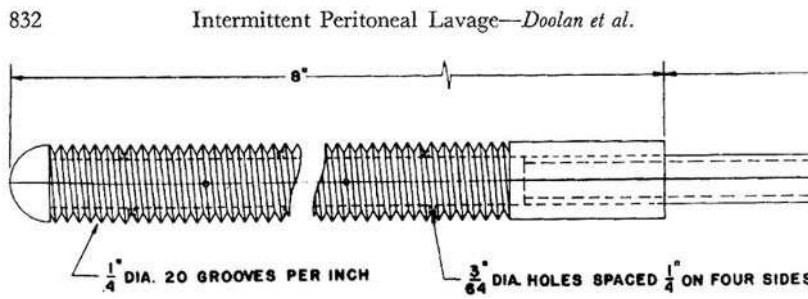

(c)

Fig. 11.16 (a) Dr. Paul Doolan (b. 1924) today, who together with Dr Richard Ruben (b) maintained the first patient long term with peritoneal dialysis in 1960 (from [44]). Doolan had described a new catheter (c) the previous year which permitted this advance (from [95] with permission. See Permissions.).

major role in the use of peritoneal dialysis during the 1960s after emigrating to Seattle in 1961 at Scribner's request, as we shall see.

Intestinal dialysis in the 1950s

In 1950 intestinal perfusion, either using intubation of the stomach or small bowel, or surgically isolated isolated loops of bowel, seemed to be a viable alternative to other forms of dialysis and was being examined in a number of centres, particularly in Paris [98]. By 1960, however, it was clear that its role was small or non-existent, for the

simple reason that the clearances of urea and other metabolites were too low to allow it alone to maintain balance and health, even at the price of prolonged treatment periods, despite some role in removing potassium in acute situations [99]. Only a few clinicians experimented with it during this decade, but the enthusiast Paul Schloerb [93,100,101] of Kansas City made careful studies of perfusion in isolated loops, which, however, only served to show to the rest of the medical world its lack of potency in removing potential uraemic toxins. Schloerb used dialysis through cellophane bags placed within the intestine to avoid the leakage problems of free perfusion, and also surgically isolated loops of bowel exteriorized to the skin, as de Leeuw had originally described 10 years previously. Apart from the group of patients treated by Clark and his colleagues [102] of the Jefferson Medical College, Philadelphia up to the mid 1960s, this technique entered the graveyard of failed medical advances, even though investigators in Paris later made the attempt to increase transport across the wall by adding agents such as bile salts to the perfusate. However, Schloerb [103] was able to point out 15 years later the still crucial role of the intestinal tract in generating uraemic toxins, as Theodor Frerichs had first suggested 120 years before.

Dialysis treatments at the end of the 1950s

Thus by the end of the decade, from being considered doubtfully useful—or even inimical—treatments, haemodialysis and peritoneal dialysis were now perceived worldwide as a necessary part of the treatment armamentarium of any major hospital in every developed country, and all had started at least a few units to administer one or another of these treatments to selected patients with acute, potentially reversible renal failure. Even children suffering acute renal failure could be treated successfully using either peritoneal dialysis [104] or haemodialysis [105]. However, it had become depressingly and agonizingly clear that, with occasional exceptions of reversible electrolyte and circulatory disturbances superimposed in patients with irreversible chronic renal failure, there was little to be gained—and much harm to be done—by dialysis. An additional role for haemodialysis, and to a lesser extent peritoneal dialysis, emerged during the 1950s also: the treatment of exogenous poisons ingested accidentally or in suicide attempts. Principally this concerned salicylates and hypnotics, old and new, such as glutethimide. In this area Paul Doolan and later his pupil and associate George Schreiner played a major role [6,74,75,106].

Many small 'renal units' were set up to take charge of patients with acute renal failure, usually in university or major city hospitals, and most of these units also became the focus of improvement in electrolyte management in general medical and surgical patients. These physicians and (in decreasing numbers) surgeons were a curious breed of half technologist, half physician-physiologist, who evolved into the nephrologists of the 1960s. Their numbers were small: worldwide, it is doubtful if there were more than 200–300 individuals involved in dialysis in 1959. In general, they were still viewed with suspicion by their more orthodox colleagues, and their position within the spectrum of general internal medicine was becoming increasingly strained. The imminent emergence of nephrology, nephrological societies and renal journals is discussed in Chapter 13.

Many different haemodialysers were in occasional use in 1959, and during the 1960s, as we shall see, the introduction of further new types of machinery continued apace and changed the face of practical dialysis completely. However in 1959 the main dialysers employed in Europe and North America were the new twin-coil kidneys (see Chapter 12) and, despite its many disadvantages, the durable rotating drum dialyser in its Boston and Parisian versions. For example, as late as 1961 in England, Frank Parsons and his colleagues [106] described an even newer version of the 1949 Boston version of Kolff's original design, with a huge membrane surface area of 3.2 m^2, which had also been installed in Glasgow, Scotland. Chris Blagg , later to be one of the stalwarts of the Seattle team in the 1960s, was a member of the group in Leeds at that time. Also in Paris, as we have seen, the 1956 Usifroid incarnation of Kolff's design was still in full use, and would initiate the long-term dialysis programme at the Hôtel Dieu Hospital in 1962. Some use was still made of the Alwall kidney especially in Sweden and central Europe, and of new flat-plate dialysers such as the Nephra II in Germany, and the MacNeill or Skeggs–Leonards dialysers in the United States (see Chapter 12), although the latter design had surprisingly little impact up to 1960.

By the end of the decade red rubber had, in general, almost entirely been replaced by the new plastics discussed in Chapter 12, but commercial regenerated cellulose acetate wrapping was still the exclusive haemodialysis membrane used, and blood access was still by metal or glass cannulas into vessels which were sacrificed after use. The innovative rubber central venovenous catheter systems which had intermittently surfaced since their first use by Murray in 1946 did not seem to have had much impact, and were repeatedly 'rediscovered' during the 1950s, and then in the 1960s [107]. But before we consider the latter decade, we need first to look at the new types of haemodialyser which took on the main load of haemodialysis sequentially during the next 25 years.

Notes and references

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elsewhere, including Spain and Italy (but not France) as well as the United States and Britain. Because of difficulties in obtaining cellophane (and other materials, the reasons for which are not clear to me), they developed a 24 micron thick 'gel cellophane' membrane together with the Kako-Seishi and Senko-Ika Corporations, which had twofold greater permeability than commercial cellophane, and used this material in their low-volume, high-performance dialyser.

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91. Polythene (short for polyethyene) was one of the early carbon-chain polymers. Low-density polyethylene was synthesized in 1935 by British chemists Eric Fawcett and Reginald Gibson using very high pressures on an ethylene–benzaldehyde mixture. Only in 1939 was it patented and produced by Imperial Chemical Industries (ICI) in the United Kingdom under the name of 'Alkathene'. During the Second World War it was used as an insulator for cables in radar apparatus, but came into widespread use in the late 1940s and 1950s in the form of sheeting. In fact Carl Shipp Marvel of the Du Pont de Nemours Inc. in the USA had also discovered the high-density form of polyethylene in 1930, but the company failed to realize the potential of the product (see: *Encyclopedia Britannica* CD-ROM article: Carbon chain polymers).
92. Letter to JSC from Pat Grollman, 2001.
93. Some of the few papers from this period are: Houck CR. Problems in maintenance of chronic bilaterally nephrectomised dog. *Am J Physiol* 1954; **176**: 175; Hulet WH. A procedure for peritoneal dialysis in renal failure. *Am J Clin Pathol* 1955; **25**: 1253; Turnbull AN. Acute renal shutdown. Report of a case treated by intravenous fluids, exchange transfusion and peritoneal dialysis. *NZ Med J* 1955; **54**: 647; Dittrich P. Die peritoneale Dialyse als klinische Behandlungsmethode. *Med Klin* 1956, **59**: 496; Schloerb PR. Peritoneal dialysis and newer methods of intestinal perfusion in renal failure. *Arch Intern Med* 1959; **102**: 914.

94. Maxwell MH, Rockney RE, Kleeman CR, Twiss EE. Peritoneal dialysis. *JAMA* 1959; **170**: 917–24. See also: McBride P. Morton Maxwell (1924–): he made acute peritoneal dialysis a routine procedure. *Perit Dial Bull* 1984: **4**: 58–9.
95. Doolan PD, Murphy WP, Wiggins RA, Carter NW, Cooper WC, Watten RH, Alpen EL. An evaluation of intermittent peritoneal lavage. *Am J Med* 1959; **26**: 831–44.
96. McBride PT. Pioneers of dialysis: Fred Boen MD (1927–). The man who brought science to the art of peritoneal dialysis. *Perit Dial Bull* 1982; **2**: 50–3.
97. Boen ST. *Peritoneal dialysis. A clinical study of factors governing its effectiveness.* V. Gorcum, Amsterdam, 1959.
98. Frank HA, Seligman HA, Fine J. Treatment of uraemia after acute renal failure by pritoneal irrigation. *JAMA* 1946; **130**: 703–5. See also: Fine J, Frank HA, Seligman AM. The treatment of acute renal failure by peritoneal irrigation. *Ann Surg* 1946; **124**: 857–75.
99. Kelley RA, Hill LD III. Acute renal insufficiency and the role of potassium with treatment by intestinal lavage. *J Urol* 1951; **66**: 645; Frey J, Fischer R. Die Behandlung der akuten Urämie mit der intestalen Perfusion. *Dtsch Med Wschr* 1956; **81**: 1671.
100. Schloerb PR. Enterodialysis. An approach to the therapy of renal substitution. *Surg Forum* 1956; **7**: 58–62.
101. Schloerb PR. The management of uremia by perfusion of an isolated jejunal segment: with observations of the dynamics of water and electrolyte exchange in the human jejunum. *J Clin Invest* 1958; **37**: 1818. See also: Schloerb 1959 [89].
102. Clark JE, Templeton JY III, Cohn HE, Soricelli RR. Isolated small-bowel dialysis in 23 patients. *Trans ASAIO* 1965; **11**: 18–21.
103. Schloerb PR. Intestinal dialysis in 1975 perspective: sorbents and intestinal nitrogen transport. *Kidney Int* 1975; 6 (Suppl 10): S248–250.
104. Moody EA. The therapeutic use of peritoneal lavage for anuria caused by toxic nephritis. *J Pediatr* 1948; **33**: 710–16. This paper from Rochester, NY appears to be the first paper to describe the use of peritoneal dialysis in an infant (aged 11 months) with severe pneumonia, who died. However in discussion of Fine's 1946 paper in *Annals of Surgery* [98], Arthur B. McGraw of Grosse Pointe, MI described peritoneal dialysis in an anuric 6-year-old with nephritis, whose outcome was still uncertain at the time of discussion. See also: Bloxsum A, Powell N. The treatment of acute temporary dysfunction of the kidneys by peritoneal irrigation. *Pediatrics* 1948; **1**: 52–7; Buerger WE, Lambert EC, Maitland AB. Peritoneal irrigation. Method of treatment of acute renal failure in an infant. *Am J Dis Child* 1949; **78**: 237; Sacrez R, Mayer G, Kern P, Deltombe J. A propos d'un cas de néphrite mercurielle traité par dialyse péritonéale. *Arch Franç Pédiatr* 1949; **6**: 547; Swan H, Gordon HH. Peritoneal lavage in the treatment of anuria in children. *Pediatrics* 1949; **4**: 586–95. Two of Swan and Gordon's little patients survived after 9 and 12 days of continuous peritoneal lavage.
105. The first child to be treated by haemodialysis was probably the 3.5-year-old included in Merrill's series in 1950 [67]. The first paper specifically dealing with this topic is: Mateer FM, Greenman L, Danowski TS. Hemodialysis of the uremic child. *Am J Dis Child* 1955; **89**: 645–55. The kidney used in three children from 6 to 14 years of age was the Westinghouse version of the Alwall kidney, which allowed low compliance for minimum and stable blood volume within the dialyser. See also: Carter FH, Aoyama S, Mercer RD, Kolff WJ. Hemodialysis in children. *J Pediatr* 1957; **51**: 125–136 who reported five children aged 2–14 years treated with single- or twin-coil dialysis.

106. Parsons FM, Hobson SM, Blagg CR, McCraken BH. Optimum time for dialysis in acute reversible renal failure. Description and value of a new large surface dialyser. *Lancet* 1961; **i**: 129–34.

107. Twardowski ZJ. Intravenous catheters for hemodialysis: historical perspective. *Int J Artif Intern Organs* 2000; **23**: 73–6. The contribution of a number of early workers such as Gordon Murray and the Italian group of Dogliotti in using the inferior vena cava is not covered in this article, although it gives a useful history of the use of subclavian and jugular venous catheters for dialysis.

Chapter 12

New designs of artificial kidney

Clearly the original artificial kidneys of the pioneer dialysers required improvement, and even in its Brigham and Usifroid forms, the rotating drum kidney still retained most of its unpleasant characteristics for both patient and physician. Design of dialysers at this time was essentially empirical, even though Kolff had used *in vitro* data to decide on how large his dialyser should be, as early as 1940. However, the goals of high blood and dialysis flow rates, countercurrent flow and turbulence in the blood and dialysate compartments had been worked out very early. Now in 1950, the process of a more formal kinetic analysis of dialyser performance began with the key papers of Wolf [1,2], almost all involving the study of the removal of urea, both because of its quantitative importance and ease of measurement, but despite its doubtful role in uraemic toxicity.

Many new dialysers

Nevertheless, design of new dialysers at best remained approximate. During the period 1947–1970, about 70 different new designs of artificial kidney were presented (Table 12.1), many little or never used, especially a number built and introduced during the early 1960s just before attention focused on only two or three basic designs. Details of most of those machines not discussed here can be found in McBride [3] or Drukker [4], and in especial detail in Dittrich [5] ,as well as in the CD of Zenker [6]. A number of now little-known early designs were widely discussed (if not widely used) at the time of their introduction, such as the flat-plate dialysers of Sterling and Doane [7] and the New York urologists Lowsley, Sterling and Kirwin (1951) [7]. These designs, along with the dialysis cell of Bartrina in 1949 [8] and the several Italian and Japanese machines dealt with above, are not mentioned or illustrated in McBride [3] or Drukker's [4] reviews, and some do not even appear in Dittrich *et al.*'s exhaustive review of machines in 1970 [5]. Stephan Rosenak of the Mt Sinai Hospital (see Chapter 5) designed no less than three machines [3], one a flat-plate model and two coils, one with dialysis tubing ingeniously threaded through and wound within polyvinyl chloride (PVC) tubing containing the dialysate—a design later exploited in the 1960s by Emilio Rotellar of Spain (see Chapter 11) in his 'glomerulus' kidney.

A few other machines are of interest for their provenance, such as the 1961 Soviet machine of Ananjew (which is illustrated in one of Alwall's articles, see Chapter 8, ref. [38]), which was a flat-plate dialyser with an integral dialysate tank below, and

Table 12.1 Main types of dialysers/dialysis systems from 1943 to 1966

Rotary dialysers
1943 Kolff–Berk
1947 Darmady–Kolff
1947 Fieschi–Kolff
1948 Vanatta–Muirhead-Grollman*
1949 Allis–Chalmers Inc
1950 Kolff–Brigham
1956 Usifroid–Kolff–Brigham
1961 Parsons–Kolff–Brigham
Spiral dialysers
Extended spiral
1944 Rhoads–Saltonstall
1946 Alwall (in canister)
1946 Murray (open)
1950 Jernstedt–Westinghouse Inc. (in canister)
1950 Moeller (in canister, grooved to allow countercurrent flow)
1953 Battezzati–Taddei
1956 Dogliotti–Battezzati–Taddei (double, grooved)
1956 Inou
1960 Gál–Németh
1966 Rotellar 'glomerulus'
Flat spiral (radial dialysate flow)
1952 Bianchi–Borghi
1952 Rosenak
Coil dialysers
1947 Von Garrelts
1948 Rosenak–Oppenheimer–Salzman*
1953 Inouye–Engelberg (in container)
1956 Kolff–Watschinger–Baxter (in container)
1955 Hillenbrand–Hoeltzenbein
1957 Sartorius
1961 Nosé
1962 Lawson–Blainey–Simpson (integral plastic container)

Table 12.1 *contd.*

1966 Hoelzenbein
1967 Patel–Levy
Parallel-flow dialysers
Sheet
1949 Skeggs–Leonards
1951 Lowsley–Kirwin
1951 Sterling–Doane–Hollander
1952 Kimoto–Shibusawa–Tango
1953 Murray–Roschlau–Halstrup
1954 Caporale–Pironti
1960 Kiil (and various modifications, e.g. Cole 1963)
1961 Niiechal
1961 Ananjev
1962 Galletti ('Klung' oxygenator-dialyser)
1963 Esmond ('Dialung' oxygenator-dialyser)
(several other plate dialysers were introduced and used during the mid 1960s, but differ only in detail from previous designs)
Tube
1947 Malinow–Korzon* (ultrafiltration not dialysis)
1951 Rosenak–Salzman
1952 Shibusawa–Tango–Kimoto
1954 MacNeill (Collins 1959)
1959 Rosenak–Kupfer
1959 Shibusawa–Tango
1960 Bluemle (cone support)
1962 AUE (Kaden–Richter)
1966 Leonard
Radial-flow dialyser
1964 Bluemle
Grooved plate capillary
1957 Kuhn
1960 Savino
1961 Zosin
1963 Longmore

Table 12.1 *contd.*

Hollow–fibre capillary
1964 Stewart–Mahon
Reversed (dialysate within tubing surrounded by blood)
1952 Guarino–Guarino
1964 Smith–Gara
Fractional dialysis (dialysis cells)
1950 Bartrina
1956 Bartrina–Németh–Gál
1957 Sorrentino (+ electrodialylsis)*

Whether or not a modification of a previous design should be included as 'new' dialyser is moot. I have listed here the early modifications and rebuilds of the Kolff rotating drum kidney because of their intrinsic interest—some such as that of Palmer in Canada (not listed) were a faithful reproduction of Kolff's designs. Others like Darmady's were complete rebuilds, using only vague instructions and a knowledge of the principle. During the 1960s a number of disposable inserts for the Kiil kidney were used, and several disposable coil kidneys and the first disposable flat-bed dialysers were introduced.
* These were not used clinically, as far as I can find.

one or two East German machines (also illustrated by Alwall), or the dialyser/oxygenators of Esmond and of Galletti in the United States (the 'klung' and 'dialung') developed in the 1960s.

The United Kingdom played only a small role in innovations in dialysis design: the cardiac surgeon and engineer Donald Longmore produced a small portable integral unit in 1960 [5], and 2 years later the group in the Queen Elizabeth Hospital in Birmingham introduced the 'Minicoil', a novel design in which a small disposable coil dialyser was encased within its own integral PVC (see below) container as a single unit, thus requiring only a dialysate supply for use. However, it had only a small area (0.6 m^2) and poor efficiency, even in its twin coil version of 1965, and did not achieve wide use—although a number of United Kingdom units tried it out for acute renal failure, including our own unit.

New materials determined the new designs

The main point of interest for the present discussion is that these machines made increasing use of new materials derived from the rapidly developing plastics industry, which were less thrombogenic and easier to work with compared with metal, rubber and glass, and could be easily moulded, although traditional materials such as brass, rubber, glass and chrome were still in evidence.

The prototype of these new materials was *polyvinylchloride* or *PVC* ($CH_2{\cdot}CH\text{-}Cl_n$), first synthesized as a rigid compound as early as 1872 by Eugen Baumann in Germany, using the toxic gas vinyl chloride as precursor, but was patented only in 1913 by Friedrich Klatte. To begin with, this compound was made in the form of a resin for

electrical insulation, often co-polymerized using vinyl acetate, as in Vinylite® from 1930 (Union Carbide—the well-known 'vinyl' of the first long-playing records). Waldo Simon of the B.F. Goodrich Company in the United States discovered accidentally in 1926 that the addition of 'plasticizers' such as butyl or other phthalates allowed flexible sheets and then tubes to be manufactured. During the early 1950s, disposable tubing made of PVC was introduced into medicine, and by the early 1960s had almost completely replaced the resterilizable red rubber and glass tubing in dialysis, as in the rest of medicine. The impact of this change can only be imagined by those who did not experience it at first hand. In addition, other materials such as nylon sheet and web, polypropylene boards, and finally polytetrafluorethylene (PTFE, Teflon®) became available. Rapidly this led to the production of commercially available disposable dialysers, the first of which was the Baxter (later Travenol) U-200 twin coil of 1956. This was the first design to become dominant, to be followed in turn by parallel-flow dialysers, and then hollow-fibre models.

The twin-coil kidney

Murray had built the first static, vertically mounted spiral kidney in 1940, and others based on this basic design were used by Alwall from 1942 in animals [9]; another coil design was presented in 1947 by Bodo von Garrelts [3,5,10] in Sweden. The importance of this type of dialyser (as Alwall was the first to realize—see Chapter 8) was that if the coil was placed within a rigid closed jacket, it permitted controlled ultrafiltration, which the open Kolff rotating drum design did not. Yet another coil kidney appeared in 1952 designed by surgeons William Inouye and Joseph Engelberg in Philadelphia [11] using a pressure cooker as the rigid outer jacket (Fig. 12.1). Kolff had by this time emigrated from the Netherlands and had settled in Cleveland, Ohio (see Chapter 11), continuing to work on artificial organs including dialysers, although his main interest was by now an artificial heart. However, provoked and helped by

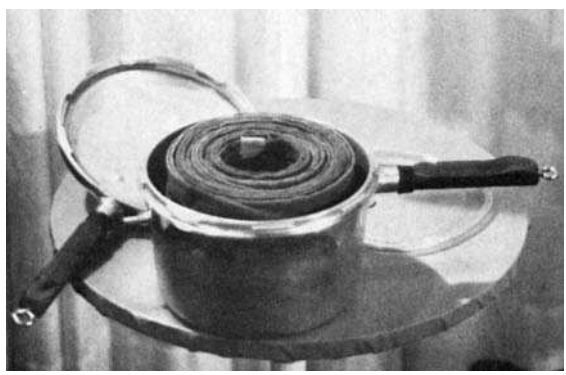
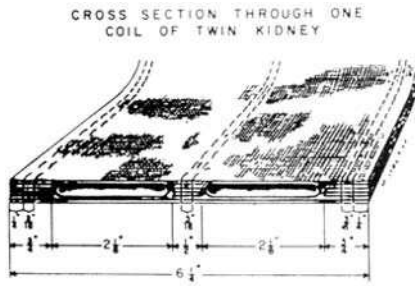
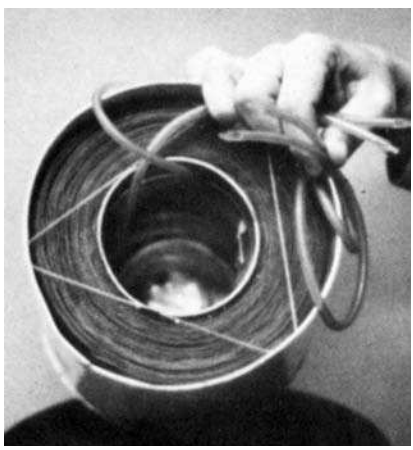


Fig. 12.1 The Engelberg–Inouye dialyser, 1952. The important feature of this model was the closed container surrounding the coil (here in the form of a domestic pressure cooker) with circulation of the dialysate, which predicted and led to the design of the twin-coil dialyser.

(a)



(b)



(c)

Fig. 12.2 (a) Bruno Watschinger (b. 1921) is shown here with his twin-coil kidney in 1957. (b) The layout of the coils. (c) The coil in its canister. (From [12].)

Bruno Watschinger of Austria (b. 1921) (Fig. 12.2a) whilst the latter was on a brief visit to Cleveland, they developed with extraordinary rapidity in 1955 [12,13] a coil dialyser based on the Inouye–Engelberg design. This utilized a nylon mesh used normally as a flyscreen for house porches and doors, as a support to flatten the two large-diameter cellophane tube coils and allow exposure to the re-circulating dialysate in a tank [12,13] (Fig. 12.2b, c). Initially, the coils were wound on to discarded pineapple cans, using a machine built in his garage by Kolff to ensure equal tension.

Involvement of industry

Up to this point only the commercially unsuccessful Allis–Chalmers version of the rotating drum kidney and the Westinghouse version of Alwall's design had entered the commercial market briefly (see Chapter 11). Kolff characteristically offered this new dialyser design as a gift to manufacturers [3], but initially had no takers, perhaps because the previous attempts had not been commercially viable. However the third company he approached, the Baxter Corporation, took it on and manufactured it as the first widely used commercial dialysing machine, the Baxter/Travenol reirculating U-200 twin-coil dialyser, the first major example of the collaboration between researchers and industry. This dialyser, together with its companion 100 L recirculating tank, became the 'work horse' of acute dialysis worldwide from the mid 1950s to the end of the 1960s, and even beyond in many units [2] (Fig. 12.3). The impact of this machine on the availability of dialysis worldwide cannot be overestimated. Instead of having to build a kidney from scratch, one could be purchased with an

Fig. 12.3 The first Baxter system designed to take the 'twin-coil' dialyser—the 'work horse' for acute renal failure, as well as for much chronic renal failure, during the late 1950s and 1960s.

easy-to-use and disposable coil dialyser and sets of tubing–but at a price which was very high for workers in many countries [14].

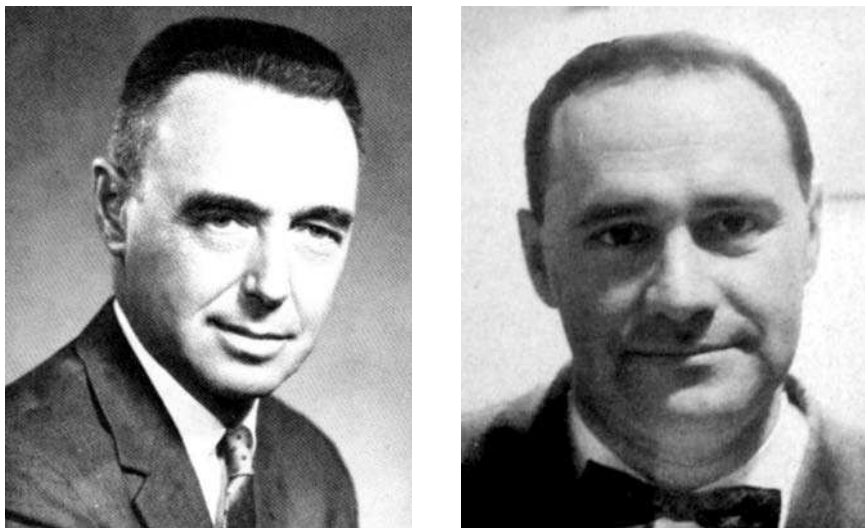
Only 10 years previously everyone had been struggling with red rubber tubing and glass or brass connectors: now thanks to PVC, plastic tubing and connectors were available also, and dialysis could be made correspondingly much easier. The dialysate had still to be prepared by hand, however, mixing dry salts with the correct volume of water.

Between 1956 and 1959 alone, Baxter's sold 123 U-200 units [3], but many—as with the Brigham kidney—were never or rarely used. The basic design of disposable coils remained essentially unchanged throughout this period until 1966, when Josef Hoelzenbein [15] in Munster, Germany introduced an improved mesh, which allowed very tight winding of the coil so as to avoid pooling of blood in the kidney and to keep the priming volume low. He had noticed, it is said, this type of stepped mesh in the design of his back garden fence, which McBride [3] illustrates—another example of 'inventors' tinkering' for the critics of dialysis as a non-scientific activity to use. To Hoelzenbein goes the credit, also, of having designed and used the first single-pass dialysate delivery system, in 1959 [3]. Hoelzenbein has been called by David Kerr 'the last of the great amateurs' in dialysis design. Up until the mid 1960s, design of machinery for dialysis was innovated by those like Hoelzenbein practising the clinical art of dialysis, with more and more commonly a subsequent involvement of industry. From the mid 1960s, however, innovation came almost entirely from within industry, although usually with close co-operation of practising nephrologists (see below and Chapter 21).

This dialogue between research and industry became dominant during subsequent decades [3,5,16,17]. Already Kolff's collaboration with Berk's enamel factory, Alwall's with the Avesta iron company (and later A.B. Gambro) and Merrill's with Fenwall Laboratories (of which Carl Walter was president) had set the trend. Early workers in dialysis often found that industry was more responsive than their medical colleagues to their ideas! Not all such early collaborations were successful, however, as we have seen. Although the Allis–Chalmers version of the Kolff rotating drum kidney [3] in Milwaukee never really got off the ground, 12 machines were made and distributed: at least one was used clinically, in Milwaukee in 1949, as van Noordwijk relates. Another was lying unused in Cleveland when Kolff arrived the following year! Nor did the Murray-designed coil kidney manufactured in Buffalo, or the Westinghouse static-coil Alwall-type kidney designed by George Jernstedt in Pittsburgh [3] succeed, even though the latter's integral design was novel and far-sighted and was used on children in Pittsburgh Children's Hospital by Mateer and Danowski (see Chapter 11) and on adults at the Veterans' Hospital in Pittsburgh [3].

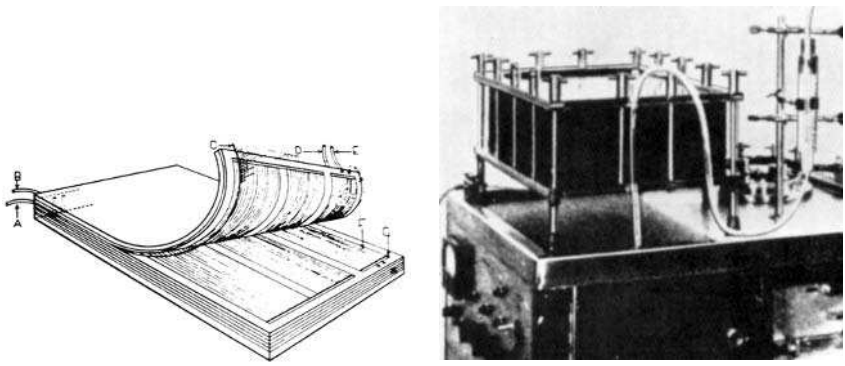
Flat-plate parallel-flow kidneys: the Skeggs–Leonards, MacNeill and Kiil kidneys

Of the three major designs of dialyser, if the coil dialyser was the design of the 1950s, the flat-plate parallel-flow design played the major role in the years from 1960 to about 1980. The first flat-plate dialyser was, of course, that of Necheles in 1924 [18],



(a) (b)

Fig. 12.4 (a) Leonard Skeggs (b. 1918) and (b) Canadian Jack Leonards (1919–1978), who developed the first flat-plate dialyser in 1948. This design was dominant from the 1960s to the 1980s. ((a) courtesy Dr Skeggs; (b) courtesy Dr George Schreiner.)



(a) (b)

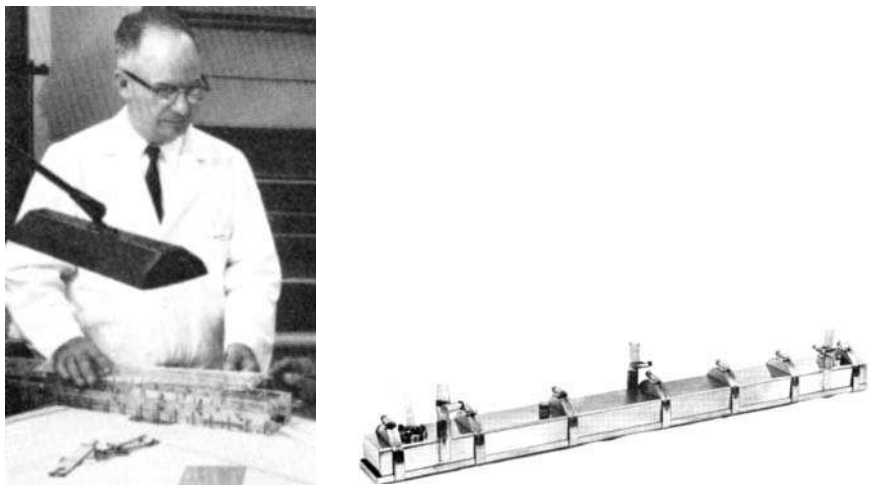
Fig. 12.5 The early Skeggs–Leonards kidney—the first practical flat-plate dialyser, which was used in the first chronic dialyses in Seattle. (a) The design of the dialyser, which drew on Skeggs' experience of automated analysis, and (b) an early model used during the 1950s in Pittsburgh; later models had fewer layers and a larger surface area to each plate. (Courtesy Dr Leonard Skeggs, from [3].)

but the first with any impact was that of chemists Leonard Skeggs (b. 1918) and Jack Leonards (1919–1978) (Fig. 12.4), who was also an MD clinician at Case Western Reserve Hospital, Cleveland, Ohio [19]. This design was first used clinically in 1949 in Cleveland, and remained in use for up to 15 years (Fig. 12.5). Skeggs [20] was an

extraordinarily talented and versatile chemist and biochemist whose work on angiotensin alone would ensure him a place in medical history [21]. He recalled recently to me [22] that he had never heard of Necheles' work, then or since—although Necheles was working not far away in the department of gastoenterology in Northwestern, Chicago by 1947. Jack Leonards had got a copy of Kolff's thesis when it appeared in 1947, and showed it excitedly to Skeggs. He thought it a magnificent paper, but felt 'they could do much better' so far as the design was concerned. The flat-plate design was conceived 'out of my head', by Skeggs with no particular reference to dialysis cells for laboratory work. Skeggs says all they had used hitherto for laboratory dialysis was bags of cellophane tubing, and he was unaware of the extensive literature on this subject. They were never in contact with MacNeill in Buffalo and were unaware of his work, which had received little publicity, and indeed was not published properly until 1956.

Hard rubber seemed to Skeggs and Leonards the best material to use because it would form a self-sealing gasket for the membrane, and was there in the first model, which had only one sheet of cellophane with blood on one side and dialysate on the other. However, there were problems with clotting, and they decided to keep the blood in contact only with cellophane by using two sheets as a blood compartment with the dialysate only in contact with the rubber on the top and bottom. Grooves on the support plate were there in the first concept. Later models multiplied the layers into a stack, and the result was a powerful but simple dialyser. The priming volume was very low, and was fixed by compression of the stack between metal plates. No blood pump was necessary to begin with. No prior calculations or experiments to determine dialysance were done—the size was worked out with trials on the bench and in dogs, then in humans. Skeggs later went on to design a radically new automatic chemical analyser for blood, using continuous dialysis and blood samples separated by bubbles (which became in 1958 the Technicon AutoAnalyser®), the prototype for almost all such machines in use today.

The next practical flat-plate design was constructed by Arthur MacNeill in Buffalo, New York (Fig. 12.6) in 1949 [23], independently of Skeggs and Leonards. His dialyser, first used clinically in 1954 in Buffalo was essentially similar to the Skeggs–Leonards model, but was much longer and narrower, as he foreshadowed in his early discussion of capillary flow [23]. This model was successively developed throughout the 1950s, largely on contracts from the US military [3] who after Korea realized the many disadvantages of the rotating drum design in practice. MacNeill's design led on to the production of disposable flat-plate dialysers 15 years later, although his early prototypes had a high thrombosis rate. Murray's now forgotten but advanced turbulent-dialysate multipoint flat-plate dialyser of early 1951, and its development in Germany during the mid 1950s by Erwin Halstrup, has been noted already in Chapter 8 [3,24,25]. Other flat-plate designs from the late 1940s and early 1950s such as those of Sterling and Doane in 1949 [7], Lowsley in New York [7], Confortini in Italy and Shibusawa in Japan have been discussed briefly already in Chapter 11. There were others, too, such as that developed by the versatile Stephen Rosenak in New York [3]. Van Noordwijk illustrates in his book a hitherto forgotten flat-plate model designed and built by Kolff himself, the 'Mieneke' kidney named after



(a) (b)

Fig. 12.6 (a) Arthur MacNeill. (b) His design of flat-plate dialyser was commissioned by the US army and was eventually used as the MacNeill–Collins dialyser in the Vietnam conflict during the 1960s. This model was also used for daily prophylactic haemodialysis by Teschan, and in early chronic dialysis in Seattle for a short while. (From [3].)

one of his technicians, which apparently was used clinically in Leiden in 1949 [26]. However, Kolff did not follow up on this, preferring the coil design for his disposable dialyser of 1956, as discussed below. Claus Brun in Copenhagen, Denmark also used a very large (4 m^2) flat-plate dialyser in the early 1950s.

In all these early flat-plate dialyser designs (Figs 12.3, 12.5 and12.6b), sheets of cellophane membrane between which blood flowed were sandwiched between grooved plates to direct countercurrent dialysate and blood flow. Resistance to blood flow was low, an important point since in contrast to the coil designs it avoided the use of a blood pump if arterial blood were used for dialysis, as was almost always the case at that time. In essence, the flat-plate dialyser was a development of the single-plate design of dialysis cells which had been used in the laboratory for decades, even if they played no direct role in Skeggs' design (see Fig. 8.6 for Halstrup's version of such a laboratory dialysis cell).

In retrospect, it is puzzling to understand why these efficient, compact, flat-plate designs with a constant low priming volume of blood had so little impact during the 1950s. Kolff's rotating drum machine continued to have all the disadvantages discussed previously, and even in its improved Brigham and Usifroid versions, retained the major problem of variable and unpredictable blood pooling within the dialyser. The British nephrologist Bill Cattell memorably described Kolff's huge rotating drum dialyser as 'the largest oil barrel you can imagine, wrapped around with tubing and thrashing around half-submerged in a horse trough'. In comparison the Skeggs–Leonard, Halstrup and MacNeill dialysers were tiny, and could be picked up and carried—although not easily with one hand! Perhaps if more powerful models had

been available, or a disposable flat-plate dialyser had been at hand in 1956 to rival the twin coil rather than appearing as late as 1968, things would have evolved differently.

The Skeggs–Leonards dialyser was used by Scribner in his initial attempts at long-term dialysis in the early 1960s, after he had tried the MacNeill–Collins model and found it less satisfactory. This latter model was adopted, however, by the Anthone twins Sydney and Roland in Buffalo during the later 1950s, as well as by the US army who supported refinement of its design and production as the MacNeill–Collins dialyser, after collaboration with Warren Collins of Boston. This MacNeill–Collins model was used by Teschan [27] and later in Vietnam in 1968 by Stone, Knepshield and others [3,28]. The influence of the US military on dialyser design was strong in the 1950s and early 1960s [29].

Then, in 1960, the Norwegian urologist Fredrik Kiil (Fig. 12.7), designed an improved, low-resistance parallel-flow apparatus which could be rebuilt, intending it primarily for use as a membrane oxygenator [30]. This dialyser (Fig. 12.8) was relatively free of clotting and could be used without a blood pump, which almost all designs hitherto had required. Moreover, it was intended to be used with a 'new' form of cellulose regenerated into sheets using the cuprammonium process (see Chapter 7), again a product of the packaging industry through the Enka Company of Bamberg, Germany, and not originally intended for medical use. This membrane was thinner and more permeable than the previous cellophane; thus a 1 m^2 dialyser had a relatively high performance, since previous flat-plate dialysers had not been very powerful. Kiil's design, brought to the United States after Claus Brun introduced Scribner to

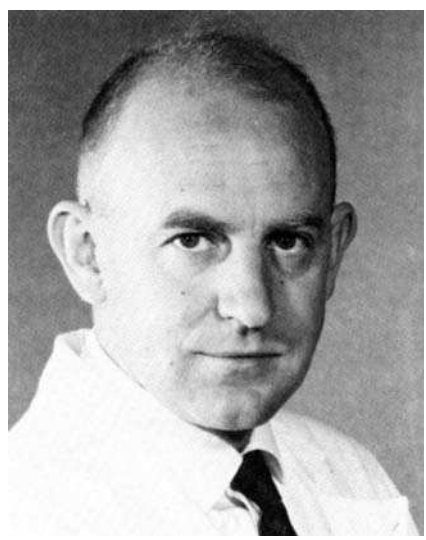
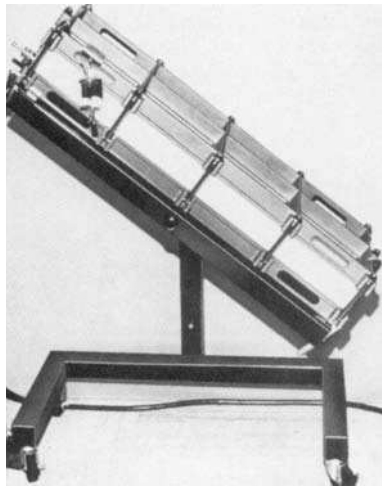
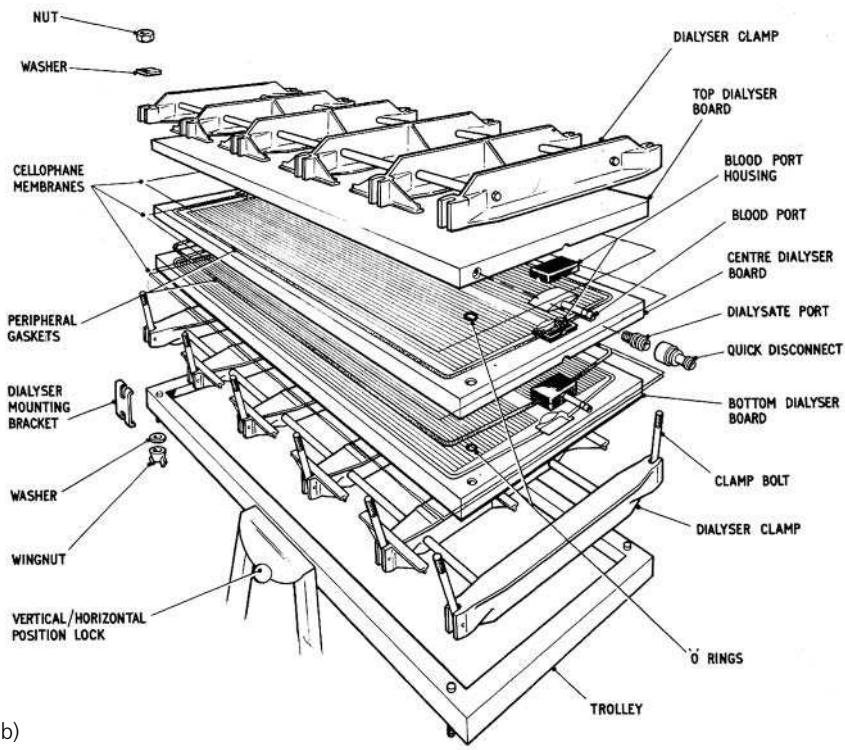


Fig. 12.7 Fredrik Kiil, the Norwegian urologist who set out to design an oxygenator but produced a design of kidney which dominated the 1960s and 1970s. This was the first dialyser to use the new cuprammonium cellulose, and set new standards of perfomance and reliability. (Courtesy Dr Fredrik Kiil, from [3].)



(a)

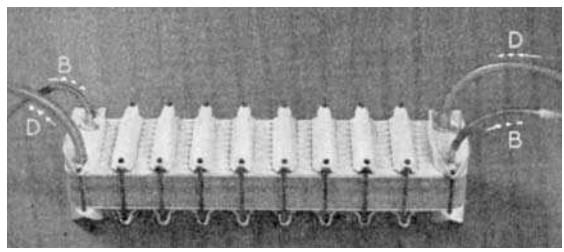


(b)

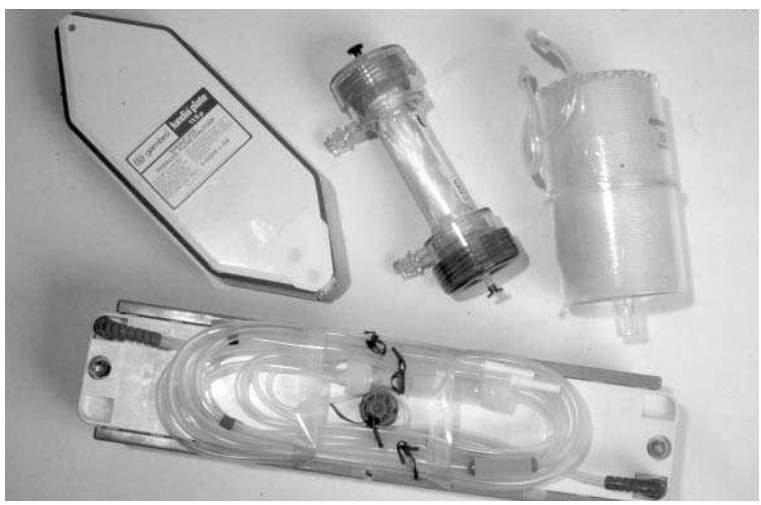
Fig. 12.8 (a) A Kiil dialyser for long-term dialysis in the 1960s. The three boards are clamped together for use with the membranes between to form the blood compartment using a frame, as in the Skeggs–Leonards kidney. (b) A later model shown 'exploded' to show the arrangement of the stack of membranes and boards, which required building before each use or alternate use.

Kiil at a meeting in Denmark in 1961, achieved worldwide use in the 1960s and 1970s for simplified pumpless home haemodialysis (see Chapters 21 and 22). Kiil, however, resented the fame that his dialyser design brought him, preferring as a urologist to be remembered for his work on ureteric motility. All these designs used grooves for the membrane support, until the Murray–Roschlau–Halstrup multipoint design was rediscovered independently in 1960 by Ed Leonard in New York and Bill Bluemle in Philadelphia [3].

In the 1960s the first flat-plate disposable dialyser based on the MacNeill design was made by Harold McDonald (then in Boston) and John Merrill [31], but this did not go into production. However, designs based on the Kiil model were introduced, first



(a)



(b)

Fig. 12.9 (a) An early disposable flat-plate dialyser constructed by A.B. Gambro to a design by Alwall, 1967–1968. The clamps were made of metal, which made the unit very heavy. (b) Lighter, all-synthetic disposable flat-plate dialysers were to become the commonest form of dialyser in the 1970s and much of the 1980s. This picture from 1973 shows two disposable flat-plate dialysers, including the Gambro Lundia (top left) as well as a disposable coil (Chron-a-Coil, top right) and a Cordis–Dow disposable capillary fibre kidney (top centre).

of all by Alwall in collaboration with theA.B. Gambro Company in Lund in 1967 (Fig. 12.9a) [9]. The early models were large, clumsy and heavy [32], and although 'disposable', the accumulating mound of these bulky dialysers in their awkward, ugly metal frames was difficult to get rid of! Soon more sophisticated models arrived with the elimination of the metal frame, so that the disposable all-plastic flat-plate model such as the Gambro Lundia (Fig. 12.9b) was available by the end of the 1960s and became the predominant type of dialyser design used in the 1970s and early 1980s, although coil dialysers continued in use in many units (see Chapter 17).

Capillary dialysers

Abel's design was an attempt to build a dialyser based upon multiple tubes, and as noted already, he and his colleagues presaged the idea of a dialyser with a 'huge number' of small tubes. The linear tube dialyser of MacNeill discussed in the previous section was in some ways a direct development of this idea, and in 1957 the Swiss H. Kuhn and his colleagues built a small (0.28 m^2) 'capillary' dialyser in which four units with tiny canals etched on plexiglass sheets sandwiched with cellophane sheets were used to produce minute canals [4].

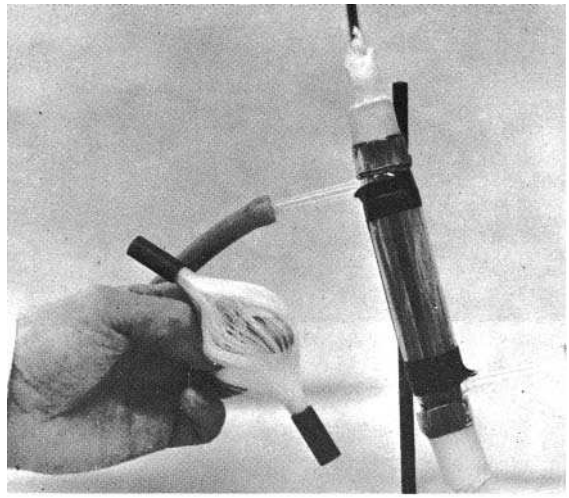
However, the difficult technology of extruding small (200 μm diameter) cellulose fibre tubing was only patented by the Dow Chemical Company in 1961 [33]—yet again, as so often throughout this history, not for medical application but originally

Fig. 12.10 Richard Stewart, who pioneered the capillary fibre kidney, now almost universally used for long-term dialysis worldwide. (Courtesy Marquette University Library.)

for industrial use, in this case for reverse osmosis systems to purify water. Richard D. Stewart (b. 1926) (Fig. 12.10), a Floridan who graduated from the Michigan University after a period in the military, first encountered the artificial kidney in the form of a flat-plate dialyser in the late 1950s. In the summer vacations whilst a student, and encouraged by the medical director Dr Harold Gay, he had worked in the Dow Corporation in Midland, MI, and after his internship he joined the staff at Dow in 1956, interrupted only by his residency at the University of Michigan in Ann Arbor 3 years later. His main interest at that time —and has remained since—was environmental toxicology, and in the mid 1960s he was working on the toxicity of chlorinated hydrocarbons and alcohol. He had many other clinical interests, however and had described (and patented) a silastic intravenous catheter in 1961, important in the development of the arteriovenous shunt (see Chapter 14, ref. [14]). He was intrigued by the capillary tubing which Dow scientist Henry I. Mahon, working in their western division in Walnut Creek, CA was now producing experimentally. Initially Stewart had the idea of making a capillary membrane oxygenator using silastic fibres, but decided to try using the new thin (14 μm) cellulose triacetate hollow fibres for dialysis, in collaboration with Mahon, with the idea of removing the chlorinated hydrocarbons which were his main clinical interest at that time; but he and Mahon realized rapidly that they could be used also to relieve the toxicity of uraemia. Stewart considered that the artificial kidneys available at that time were clumsy, ineffective and too complicated, especially if they were to be used by patients themselves at home. Any patient who had ever built, rebuilt and built yet again a Kiil dialyser would have endorsed that opinion fivefold. Stewart's 'kidney' was planned to have the advantages of low priming volume, large surface area, consistent permeability and no requirement for a blood pump.

By 1964 Stewart and Mahon, together with urologist Joseph Cerny of the University of Michigan, had built an 800-fibre apparatus for dialysing blood *in vitro* [34]. A 1000-fibre model (Fig. 12.11a) was extensively evaluated *in vitro* and in dogs in 1965–1966 [35] by the same team, together with Edward Baretta (also of the midland branch of the Dow Corporation), which proved superior to existing models for both dialysis and ultrafiltration. The construction of these dialysers was made possible by the new availablity of silicone rubber (another Dow development) to seal the fibres in place at each end of the dialyser as a bundle.

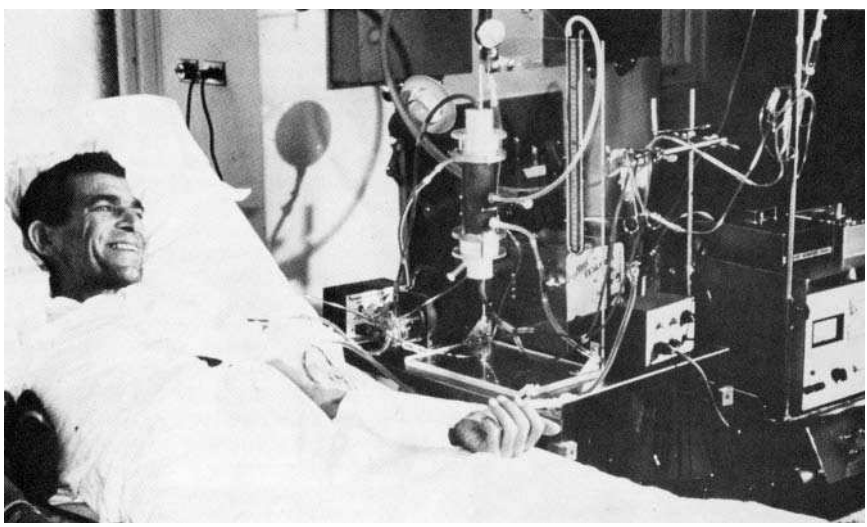
By 1967, Stewart had left Dow when his mentor Dr Gay retired, and was working in Marquette School of Medicine, Milwaukee as professor of preventative medicine and toxicology. The Dow Corporation had not been keen on the project of a hollow-fibre dialyser to begin with (although they did suggest calling it the 'Stewart dialyser', an offer which Stewart rejected) [36] but the company decided that the research work on the project should continue, but in its western division in California. Stewart and the western division Dow team in Walnut Creek, including Drs John Sargent and Ben Lipps, managed to scale up the dialyser and by 1967 had constructed an 8000-fibre 1 m^2 model [37] which was tested first on dogs. Then an 11 000-fibre model was used clinically in a patient [38] (Fig. 12.11b) on 15 August 1967 for only 1 hour; 2 days later a full dialysis was done on the same patient with success. During 1968 the team led by Stewart now included two nephrologists, Walter Piering and Donald Roth, and



New Renal Dialyzer Tested

An experimental artificial kidney composed of approximately 1,0 fine plastic capillary tubes sealed in a glass chamber has been d veloped by investigators at the Dow Chemical Company, Michiga

(a)



(b)

Fig. 12.11 (a) Stewart's 1000-fibre capillary dialyser used first in dog studies in 1965–1956, and (b) the first full dialysis in a human subject using an 11 000-fibre model, 17 August 1967. The revolutionary new dialyser is top centre in the picture. (Courtesy Dr Stewart.)

reported successful dialysis of a series of patients at the Milwaukee Regional Medical Center and the Woods VA Hospital [39]. An 'artificial capillary lung' was also tested that year [40].

The design of the dialyser was advanced further by Lipps and Sargent in California, working together with Frank Gotch and his colleagues at the San Francisco General Hospital [41] who had a close relationship with the Dow Corporation. With the transfer of all the work on the project to the West coast by Dow, Stewart continued in Milwaukee with his first love of industrial and environmental epidemiology and pollutants, heading the Department of Environmental Medicine at Marquette (later the Medical College of Wisconsin). During the following 20 years he did no more work in the field of dialysis, although he published extensively in his chosen fields.

The capillary fibre dialyser had its teething problems like any innovation: these mainly centred around unequal perfusion of the fibre bundle, and clotting within the tiny capillaries, but by 1972 these problems had largely been solved by Lipps, Gotch and their associates [42] and the now-familiar hollow-fibre artifical kidney (HFAK) dialyser (Fig. 12.9) was in increasing use. It is worth noting again that from this point onwards in the history of dialysis, almost all dialyser design and innovation took place primarily within industry rather than by clinicians tinkering in labs in hospitals, as in the 1950s and early 1960s.

Dick Stewart's legacy is that today, almost 100% of three-quarters of a million patients worldwide on dialysis (see Chapter 21) use dialysers based on his original design (Table 12.2). This has arisen entirely within the past 30 years: in Europe in 1970 the European Dialysis and Transplant Association (EDTA) registry data show that only 2% of patients used hollow-fibre dialysers, whilst 48% were still using a coil and the remainder—more than half—one or other parallel-plate dialyser, 20% of the

Table 12.2 Dialyser used (%) in Europe 1970–1990

Year	Flat plate		Coil	Hollow fibre	Haemofilter
	Reusable	Disposable	(all disposable)		
1970	64.0*		48.0*	2.0	–
1975	13.7	40.2	35.2	10.4	<0.1
1980	3.1	45.7	16.6	34.6	1.2
1985	0.4	25.4	2.7	69.4	2.0
1990	0.2	14.2	0.1	83.7	1.8
1992†	–	6.4	–	93.6	?‡
2000	?				

From Woffinden C, Hoenich N. Hemodialysers and associated devices. In: *The replacement of renal function by dialysis, 4th edn*. Jacobs C, Kjellstrand CM, Koch KM, Winchester J, eds. Kluwer Academic, Dordrecht, 1995: 188–230, and previous editions of the same chapter.

* 13% of units used both types of dialyser.

† The last year for which pan-European data are available.

‡ In the 1991 EDTA registry report a total of 5.8% of patients were stated to be receiving haemo(dia)filtration treatment.

Kiil rebuildable type, the remainder disposable designs. But by 1982, capillary-fibre dialysers had passed the 50% mark, and by 1990 the 90% mark.

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Chapter 13

The role of dialysis technology in the founding of nephrology

During the first half of the twentieth century, medicine had shown a tendency to spawn specialist groups of physicians interested in particular groups of diseases, usually based upon an anatomo-physiological system: first dermatology in the late nineteenth century, then neurology, cardiology and later gastroenterology. However, between the two world wars the study of renal disease remained within the province of general physicians such as Henry Christian, Arthur Fishberg, Thomas Addis and Leonard Rowntree in the United States, and Franz Volhard, Pasteur Vallery-Radot and Robert Platt in Europe; whilst renal physiology remained fully integrated with physiology in general.

One can chart the emergence of nephrology by two sets of events: the formation of societies devoted to the specialty [1–9] and by the appearance of new journals devoted exclusively or predominantly to nephrological subjects. These data are shown in Table 13.1 and they demonstrate that by these criteria, 'nephrology' emerged during the 1950s and 1960s: the question remains, why then?

There is probably no simple answer to this question. Certainly the initial impulse came from physiologists, pathologists and physician-surgeons interested in the function of the organ in health and disease. In physiology, the work of American physiologists led by Homer Smith had placed kidney function on a new level of understanding and accuracy during the 1930s and 1940s [10]. The transfer and understanding of electrolyte, acid–base and water physiology into the clinic was well ahead by the end of the Second World War, prompted by new concepts, but also by the introduction of the flame photometer to clinical medicine in 1947 (see Chapter 10). In the United States James Gamble, John Peters and Stanley Bradley amongst others, in the United Kingdom Douglas Black and Malcolm Milne, and in French-speaking countries René Mach and Jean Hamburger applied the principles of physiology to the study of clinical renal disease and electrolyte disorders. In pathology in the United Kingdom and above all the United States, Jean Oliver, Addis, Arthur Ellis, Paul Kimmelstiel, Clifford Wilson, E. Bell and Arthur Allen had built on the work of Theodor Fahr and had improved the descriptions and nosology of renal pathology, although the pathogenesis of most renal diseases remained obstinately obscure. By 1950 there was a critical mass, at least from an international perspective, to promote gatherings of several dozen individuals to exchange views, ideas and new data on the kidney and its function in health and diseases, the first of which was the meeting

Table 13.1 Early societies and journals devoted to nephrology

	Society	Scope	Reference
1949	Société de Pathologie Rénale[1]	Francophone countries	[2]
1950	Renal Association	United Kingdom[2]	[3]
1950	National Nephrosis Foundation[3]	USA	[1]
1955	American Society for Artificial Internal Organs	USA and Canada	[1]
1957	Società Italiana di Nefrologia	Italy	[4]
1957	Danish Society of Nephrology[4]	Denmark	
1960	International Society of Nephrology	Worldwide	[5]
1960	Sociedad Argentina de Nefrología	Argentina	[6]
1960	Sociedad Brasilero de Nefrologia	Brazil	[7]
1961	Gesellschaft für Nephrologie	German-speaking countries	
1964	European Dialysis and Transplant Association	Europe	[8]
1964	Sociedad Española de Nefrología	Spain	[9]
1966	American Society of Nephrology	USA, Canada and Mexico	[1]
	Journal	**Language(s)**	**Country**
1954	*Minerva Nefrologica*[5]	Italian	Italy
1955	*Transactions of the ASAIO*[6]	English	USA
1963	*Nephron*[7,8]	English/French	Switzerland
1964	*Proceedings of the EDTA*[9]	English/French	UK
1971	*Nieren- und Hochdruckkrankheiten*8	German	Germany
1971	*Kidney International*[7]	English/French	Germany
1973	*Clinical Nephrology*[8]	English	Germany
1976	*Dialysis Transplantation*[8]	English	USA
1976	*Artificial Organs*	English	USA
1977	*International Journal of Artificial Internal Organs*	English	
1977	*Journal of Dialysis*	English	USA
And			
1963	*Actualités Néphrologiques de L'Hôpital Necker* (annual)[8]	French (from 1969 also English)	France
1965	*Contributions to Nephrology* (irregular)[8]	English	Switzerland

[4] All other current nephrological journals began after 1980; all three bilingual journals eventually became monolingual English publications

[1] Became the Société de Néphrologie in 1959.

[2] Had many regular and honorary members from Europe, and even the United States, and organized an international meeting on nephrology in London (1953) [3].

Table 13.1—(*continued*)

[3] Ran until the early 1960s an annual meeting, which widened its remit to other renal diseases. One of the forerunners of the American National Kidney Foundation (NKF) founded in 1961.

[4] A Danish kidney club met from approximately 1952 to 1955 under the stimulus of J. Bing and Poul Iversen, but this ceased and there was a gap before the proper founding of the national society (Steen Olsen, personal communication).

[5] Initially this was a supplement to *Minerva Medica*.

[6] Became *ASAIO Journal* in 1988.

[7] *Nephron* was the official journal of the ISN from 1963 to 1971, when after a dispute with the publisher, who retained the name and continued to publish the journal, the ISN journal became *Kidney International* [5].

[8] Journals owned and distributed by independent publishers, i.e. are not the organ of any medical or scientific society.

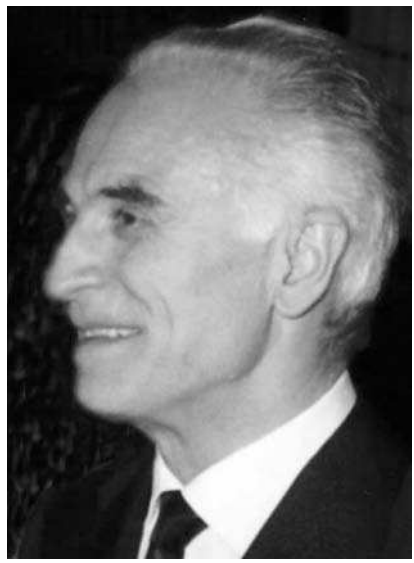
[9] Became the journal *Nephrology Dialysis Transplantation* in 1984.

organized in London in 1953 by the newborn UK Renal Association and the Ciba Foundation [3,11].

Yet, following a suggestion from Jean Hamburger, who circulated the few organizations or clubs concerned with the kidney in Europe in 1956, within only a decade more than 300 individuals attended the first meeting of the nascent International Society of Nephrology in Evian in 1960 (Fig. 13.1). Just 6 years later, for its third meeting in Washington, George Schreiner was able to identify more than 10 000 individuals to contact worldwide, of whom 2134 actually registered for the meeting [1]. The reasons for this explosive growth must have involved the new technologies that had transformed the study and treatment of kidney diseases. The influence of renal biopsy and its interpretation on the emergence of nephrology has been written about elsewhere [12]. It seems almost certain that the introduction of dialysis was an important motor which accelerated the emergence of nephrology as a speciality. Suddenly, there was a need for specialist knowledge to apply the complex data from the increasing number of critically ill patients surviving their primary disease only to go into acute renal failure. Once haemodialysis and then peritoneal dialysis had become accepted as a technique for its treatment, the need for skills to manage these complex clinical problems and run the machines increased several fold. From no units at all in the 1950s, about 250 had been started by 1962 in the United States and possibly 100 in Europe—it is more difficult to obtain data this side of the Atlantic for years prior to 1965. Then, in 1960, (as we shall see in Chapters 14 and 15), long-term dialysis became possible. Within 5 years, in every developed country, many more units were started and physicians trained frantically to run them: they were a new breed—nephrologists. In almost every case, one of the skills they possessed was the ability to treat patients by dialysis, usually through running the dialysis procedure themselves, from start up to cleaning down; they also had to service and sometimes build the machine and in a few cases, even design it.

To begin with, the relationship of this new breed of physicians with surgery, and particularly urology, was perhaps stronger than with internal medicine. The culture of the renal units involved with dialysis was 'active' rather than contemplative, and different from units mainly concerned with laboratory-based renal research. As outlined in previous chapters, gradually this urological involvement with dialysis waned during the 1960s and disappeared almost everywhere during the 1970s, leaving

(a)



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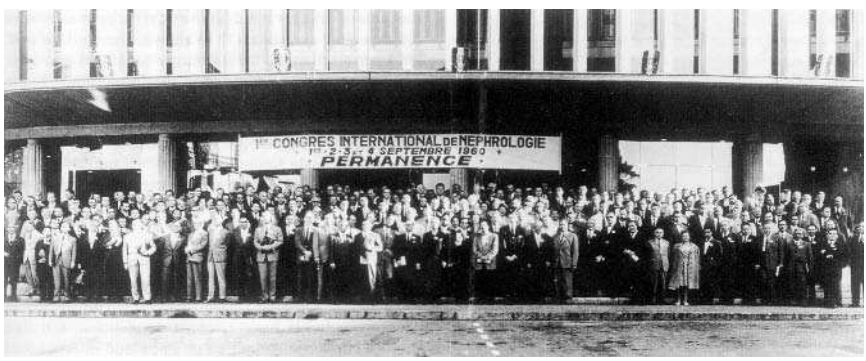

(c)

Fig. 13.1 (a) Jean Hamburger (1906–1992) of France, who first suggested an international meeting in nephrology in 1956, and saw this come to fruition in 1960 with the formation of the International Society of Nephrology (ISN) at Evian. (b) Luigi Migone (b. 1912) of Italy, who played a major role in the formation of both the Società Italiana di Nefrologia in 1957 and the ISN in 1960. Both these individuals played a major role also in the introduction of dialysis in their respective countries during the 1950s and 1960s. (c) Delegates at the first meeting of the ISN, Evian 1960, at which dialysis was extensively discussed. (Courtesy Professor J-M. Suc.)

nephrology as an autonomous specialty with an uneasy relationship to general internal medicine. There is no doubt that those physicians who chose to make dialysis their principal interest were to some extent a breed apart, with whom physicians in general found it particularly difficult to relate.

The new speciality was characterized also by the internal divide within nephrology which has been mentioned in Chapters 10 and 11: that between the 'clinician-scientists' and the 'dialysers', which in some countries expressed itself in the formation of additional splinter groups and even formal societies and journals dealing exclusively with dialysis. In general, international bodies and journals such as the International Society of Nephrology (ISN) and its journal *Nephron* (published as *Kidney International* from 1972 [13]) continued to accommodate material and the discussion of all aspects of nephrology, including dialysis. The American Society of Nephrology (ASN), formed rather late in 1966, was solidly based in laboratory research and the study of parenchymatous renal disease, and had initially rather limited involvement with dialysis. This may have been because the strong American Society for Artificial Internal Organs (ASAIO) was already 11 years old, and had already adopted the role as the usual forum for the dialysis community in the United States to present and discuss its work [1].

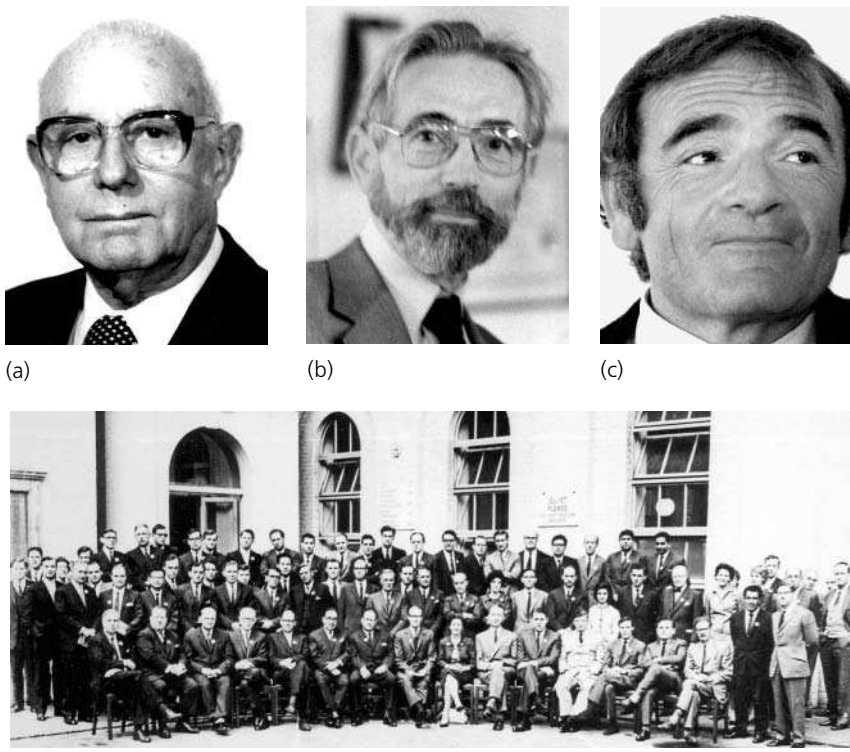

Fig. 13.2 The three co-founders of the European Dialysis and Transplantation Association in 1964: (a) William Drukker (1910–1992), (b) David Kerr (b. 1927), and (c) Stanley Shaldon (b. 1931). (d) The formation of the European Dialysis and Transplant Association first suggested at this meeting on acute renal failure and its treatment by dialysis was organized by Shaldon and held at the Royal Free Hospital, London in 1963. (See: *Lancet* 1963; **ii**: 633; Shaldon S, ed. *Acute renal failure. A symposium*. Blackwell, London, 1964.)

The position in Europe was rather different [8]. The first suggestions for a European group of nephrologists came in 1963 (Fig. 13.2) and were centred exclusively on dialysis, then after further discussion, dialysis together with transplantation, so the name of the new society became the European Dialysis and Transplant Association (EDTA). Only as late as 1984 were the words 'European Renal Association' (ERA) added, with the idea that this title eventually should replace the former. As a result, general nephrology in Europe as a whole had no ready forum at a local level for some years, whilst dialysis had a clear focus and voice.

Despite the wish for inclusiveness on the part of the ISN, the ASN and the EDTA-ERA, groups concerned principally with dialysis and related techniques grew up—the European and International Society for Artificial Internal Organs in the image of the successful American society, then with the growth of peritoneal dialysis in the form of continuous ambulatory peritoneal dialysis (CAPD) (see Chapter 19) during the 1980s, the International and then European Societies of Peritoneal Dialysis. Nor is the process of splintering complete—the beginning of the twenty-first century saw the foundation of an International Society for Haemodialysis concerned with the renaissance of home haemodialysis, often on a daily basis.

This splitting away of dialysis to some extent from nephrology was expressed again in new journals. Early on in the United States the *Dialysis Forum* had provided such an outlet during the 1960s, and a number of other informal newsletters circulated

Table 13.2 More recent journals of nephrology, 1980 onwards

General	
1980	*American Journal of Nephrology**
1980	*Seminars in Nephrology**
1982	*American Journal of Kidney Diseases*
1986	*Pediatric Nephrology*
1986	*Nephrology Dialysis Transplantation 1986* (ex *Proceedings of the EDTA-ERA*)
1988	*Journal of Nephrology*
1989	*Journal of the American Society of Nephrology*
1994	*Nephrology*
1995	*Experimental Nephrology**
Dialysis related	
1981	*Peritoneal Dialysis Bulletin* (changed to *Peritoneal Dialysis International* in 1988)
1982	*Blood Purification*
1989	*Seminars in Dialysis**
1996	*Home Haemodialysis International*

All of the above are published in English.

* Journals owned and distributed by independent publishers, i.e. are not the organ of any medical or scientific society.

within the dialysis community, many sponsored or even published by the commercial firms now entering the dialysis field in increasing numbers, such as the *Sweden Freezer News*. From 1980 onwards also, a number of formally published new journals have been started (Table 13.2), many of them exclusively dealing with dialysis. Probably the most important of these new exclusively dialysis-related journals was the *Peritoneal Dialysis Bulletin* in 1981, re-incarnated as *Peritoneal Dialysis International* in 1987. In the 1990s, the new interest in home daily dialysis spawned *Home Haemodialysis International*.

Within even the community of those doing dialysis there was—and is–heterogeneity, with different proportions of individual doctors conforming to one of three main types from country to country. Some dialysis physicians work almost exclusively with dialysis patients, either as employees of a state-run system, or within a commercial provider of dialysis (see Chapter 22). Others are general physicians in consulting practice, who in addition run or work in (often smaller) dialysis units. Then there are general nephrologists who consult on all forms of renal disease, often in hypertension as well, and are also involved with the care of dialysis patients and transplant recipients—'all-round' nephrologists. Finally, during the 1990s, within the community of nephrologists has grown up yet another group, those whose main or even exclusive interest is the management of patients following transplantation—'transplant physicians', who already have their own national association in the United States and whose meetings are attended also by those with similar interests from Europe.

Within paediatrics, in parallel but rather later than within internal medicine, came the emergence and recognition of paediatric nephrology and paediatric nephrologists [14,15]. The formal starting point of paediatric nephrology was the international group of paediatricians headed by Henry Barnett (b. 1911) of New York, the International Study of Kidney Disease in Childhood (ISKDC). Members of this group (itself started in London in 1965) began the American, European and Japanese Societies of Paediatric Nephrology in 1966–1967. A few years later in 1971 these three societies sponsored in turn the formation of the International Society for Pediatric Nephrology (IPNA) and its journal, *Pediatric Nephrology*, from 1985. In the field of paediatrics the need for dialysis played a smaller role than in adult medicine as a motor driving the emergence of the specialty. Whilst one can argue that from within internal medicine dialysis was a major force in the formation of the speciality of nephrology, it was in contrast only one of many other strands leading to the formation of paediatric nephrology.

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discourse for more than 20 years following its foundation, and vigorously turned down a suggestion for a meeting on the topic from Frank Parsons in 1959. As a result, UK dialysis physicians used the EDTA as their forum from 1964 onwards and ignored the Renal Association, to the detriment of British nephrology.

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Chapter 14

New materials and new methods of access I: long-term haemodialysis becomes possible

From the beginning of haemodialysis, physicians realized that in many patients with acute renal failure one dialysis was not enough, and sought to gain repeated access to the circulation, but without success. From 1946 to 1960, methods of connecting the patient's circulation to the various forms of artificial kidney available stagnated. Almost everywhere, following Kolff's lead, glass was employed as the cannulating material, and arteries as well as veins were sacrificed after a single use. Only a double-cannula system using the new PTFE (see below) showed any promise; this used a heparin flush between dialyses, introduced by Paul Teschan to perform daily prophylactic haemodialysis in exceptionally catabolic patients [1]. Some had success with double-lumen catheters placed within the inferior vena cava for repeated access, for example the Italian group led by Dogliotti in 1957 [2].

The external arteriovenous shunt

However, as far back as 1948, Nils Alwall had tried to join the peripheral glass venous and arterial cannulae together with rubber tubing between dialyses to form a continuously flowing shunt in order to avoid the problem (Fig. 14.1), but both in rabbits

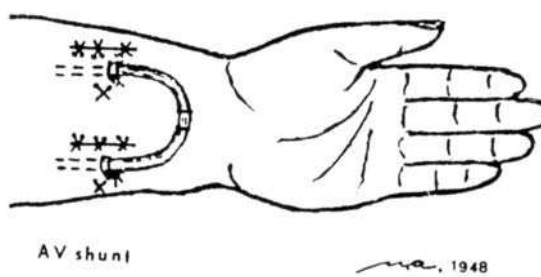


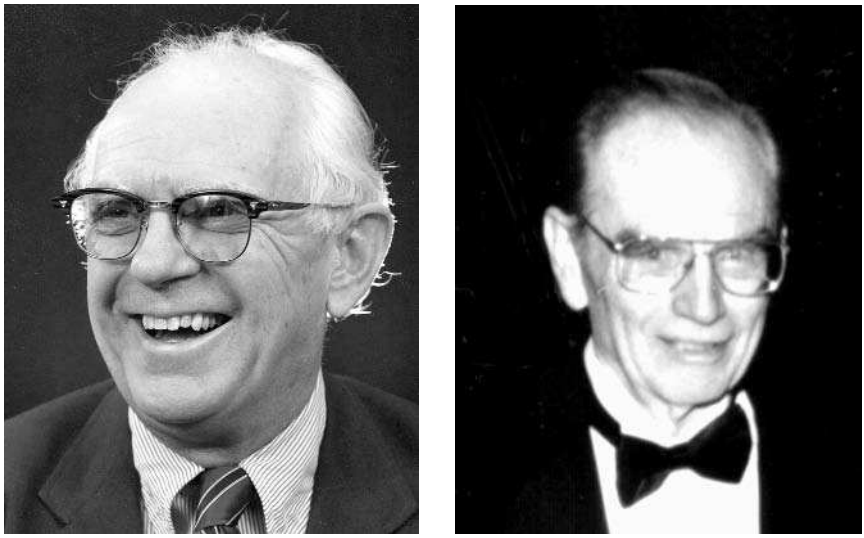
Fig. 14.1 Alwall's sketch of a glass and rubber arteriovenous shunt in 1948. Only lack of suitable non-thrombogenic materials prevented this from become a useful advance. (From [1].)

and in humans [3–5] he found that they always clotted after a few uses. He deserves credit for having first thought of the application of an arteriovenous shunt, but he could not carry the idea through to its practical conclusion, purely because of the materials at his disposal. Nevertheless, even using a coil kidney and glass cannulae for access Jack Maher, George Schreiner and James Waters [6], similar to several other groups including that of John Merrill, were able to maintain patients for many weeks—in the case of Schreiner's group for up to 6 months, before there was simply no more access.

Thus by the middle 1950s, chronic renal failure had become firmly established in almost everyone's mind as a contraindication to dialysis. It is interesting to recollect again that all the pioneers of dialysis originally intended it for repeated use in patients with *chronic* renal failure. Then its lack of success in prolonging life in these patients, and the impossibility of unlimited dialysis because of access problems led to the technique being limited to acute, potentially reversible renal failure. John Merrill has testified to the fact that by 1960 almost all physicians had become blinkered and considered dialysis in the short term only; irreversible renal failure was considered to be an absolute contraindication to dialysis, unless potentially reversible acute features could be identified in addition. Dialysis was abandoned if wholly irreversible disease was identified as the cause of the renal failure, condemning the unfortunate patient to death within a few days. This apparently cruel fate, however, was in order to avoid the even more cruel outcome of a slow death prolonged by repeated and progressively inadequate dialysis, an experience which Merrill and many others had had during the 1950s when they failed correctly to identify the potential outcome of some patients.

Yet again we find that the solution to this clinical dilemma lay entirely elsewhere, in the polymer industry. In 1938, an employee of Dupont in Deepwater, New Jersey, Roy Plunkett (b. 1910), noted by accident that a tank of the gas tetrafluoroethylene, kept accidentally under pressure and at low temperature, had thrown down a white powder: this was *polytetrafluoroethylene* or PTFE ($CF_3{\cdot}(CF_2)_n{\cdot}CF_3$) [7], usually called Teflon®. It was used to a limited extent during the Second World War as a corrosion-resistant surface, but its properties of low wettability, smoothness and strength led to its being patented in 1945 and used (like polyvinyl chloride, PVC) for electrical insulation. Bonding to aluminium in 1955 allowed its use for non-stick saucepans, and the next decade saw a steady development in the uses of the compound, as the ability to manipulate and form it increased. It was used also in 1956 as a membrane in extracorporeal oxygenators. In 1959, with major consequences for dialysis, PTFE tubing became available—but only in straight lengths—for use as electrical conduits. Indeed it can be said that the search for better electrical insulation, together with sausage manufacture, has done more for patients in renal failure than all the purely medical research invested in the subject.

In a story now told many times, Belding Scribner (b. 1921) (Fig. 14.2a) and his colleagues in Seattle, Washington brought about a major revolution. Scribner had trained in the University of California, and then at Stanford from 1941 to 1947 where he worked with Thomas Addis. Whilst at the Mayo Clinic in 1947–1951 his interest in renal disease was reinforced by a talk he attended given by John Merrill, on acute renal failure and its treatment, since at that time he was working on estimation of elec-

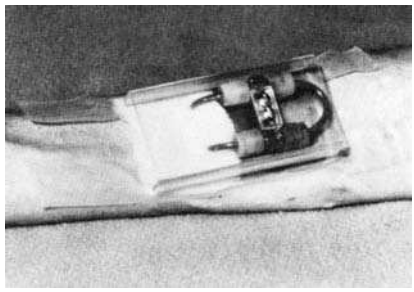


(a) (b)

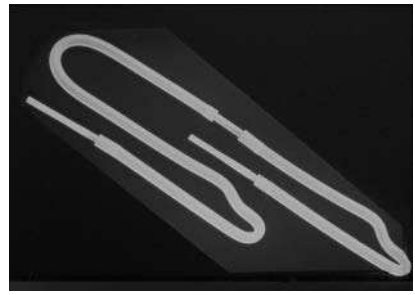
Fig. 14.2 (a) Belding Scribner ('Scrib') (b. 1921) in the 1970s, and (b) Wayne Quinton in 1998. Using new materials, through their work the re-usable shunt at last became a reality. They were initially unaware of Alwall's pioneering efforts. Although opening up long-term treatment for thousands, shunts were in use only for a decade or less before being replaced by arteriovenous fistulae. ((a) courtesy Dr Scribner.)

trolyte concentrations in plasma, trying to bring these (then still obscure) measurements from the laboratory closer to the bedside. In 1951 he left Rochester for Seattle, where later he founded the nephrology unit in 1958, and remained there for the rest of his working life. He had spent also a year in London working with Malcolm Milne on amino acids in 1957–1958, and there developed a lifelong taste for French wine. His first published paper on dialysis was published only in 1958, not on haemodialysis but gastrodialysis, then just reaching the end of its brief and undistinguished career (see Chapter 11) [8]. He estimated continuous gastrodialysis to be equivalent to only one haemodialysis per week in terms of nitrogen removal, although it was more effective in correcting acidosis, as might be expected from the loss of acid gastric juice from the body. The apparatus he developed to do continuous gastrodialysis was later cannibalized, however, to prepare fluid for continuous peritoneal dialysis (see Chapter 15).

At the same time he also pursued the use of continuous haemodialysis for supposedly acute renal failure [9], finding this could restore a considerable degree of health to those who turned out, sadly, to have terminal irreversible uraemia. As with almost all the pioneers of dialysis one particular patient, Joe Saunders of Spokane, WA who died because of Scribner's inability to prolong treatment had a major influence on his thinking and led to the new development [10]. To achieve long-term dialysis it was clear that better access than that available was needed. Scribner has



(a)



(b)

Fig. 14.3 (a) The 1960, first all-PTFE version of the Quinton–Scribner shunt (from [11]. (b) The 1966 version of the arteriovenous shunt, made almost entirely of silicone rubber, with only the vessel tips and connector made of PTFE.

stated on many occasions that he did not at that time know of Alwall's attempt to form an arteriovenous fistula 12 years previously, saying that [10], 'if I had known it would have been so much trouble, I would never have attempted it!'; in some accounts it is stated that the idea of a shunt came to him during sleep. Warren Wintershide, a Seattle surgeon, drew Scribner's attention to PTFE tubing, and Wayne Quinton

(a)

(b)

Fig. 14.4 (a) Clyde Shields, the first patient to receive a Quinton–Scribner shunt in March 1960; he was later transplanted, and died in 1971 of a myocardial infarction (courtesy Dr Scribner, from [2]). (b) Scribner with his first three patients after 10 years on dialysis in March 1970: left, Harvey Gentry; centre, Clyde Shields and Dr Scribner; right, Robin Heming (from *Sweden Freezer News* 1970; **7** (3)).

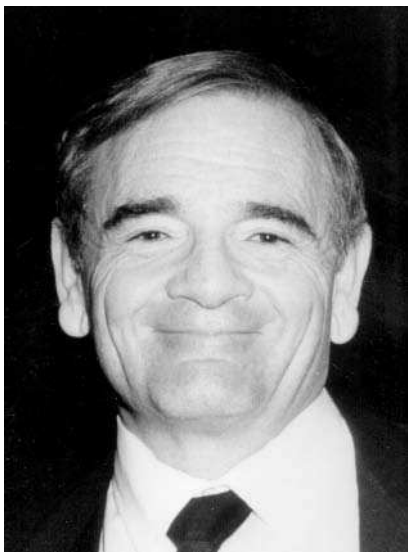
(Fig. 14.2b), an engineer who was head of the Medical Instruments Facility, was able to bend the tubing for the first time using sintering by heat (Teflon decomposes only at 450–500°C). It could then be used as an arteriovenous shunt (Fig. 14.3a), for surgeon David Dillard to implant [11]: the first two patients were dialysed using the new approach in March 1960 (Fig. 14.4)—to begin with only once a week whilst taking a reduced, 40 g per 24 hours, protein diet—but both patients' condition improved [12], one to survive for 11 years on dialysis, the second to live on until 1987 after transplantation in 1968. No controlled, randomized prospective trials or meta-analyses were done, or were needed. A warning for the future amongst this success, however, was the fact that both patients died much later of myocardial ischaemia.

The breakthrough was not simply a technical one, however. The importance of the Seattle group's achievement was the *pyschological* one of destroying the apparent barrier to more or less unlimited duration of dialysis. Very few physicians in 1960 envisaged dialysis as a future treatment for chronic renal failure—renal transplantation seemed much more promising at that time, despite the obvious problems of rejection (other than in identical twins) experienced up to that time, and this remained true for some years afterwards. Then suddenly, long-term repeated dialysis became a possibility, with all its myriad implications. The news spread rapidly around the world [13] after Scribner brought his first patient, Clyde Shields (Fig. 14.4), and Shields' mother to the 1960 meeting of the American Society for Artificial Internal Organs (ASAIO), even though they had no formal paper to present on that occasion. The editor of the proceedings of the society, George Schreiner, bent the rules and allowed a paper on the new access technique to appear in the account of work at the conference.

In some ways an even greater achievement of Scribner and his colleagues was immediately to identify, describe, discuss and begin to treat what were to become the major preoccupations of long-term dialysis: volume overload and hypertension, anaemia, high plasma phosphate concentrations and bone disease (see Chapter 16).

The rigid early all-PTFE cannulae did not last too long, but during the next 2 years Quinton struggled, and then was successful in producing internally polished tubing made of another new compound: *silicone rubber*. Silicone, a polymer of methyl silicate [14], had originally been synthesized by J.R. Hyde of the Corning glass works some time in the 1930s. The higher molecular weight polymers of silicone are gums at room temperature, which permitted the synthesis of 'silicone rubber', patented about the same time as PTFE by the General Electric Company in 1944. It was inert and non-wettable, and had been used for insulation, like PTFE, before entering the medical field about 1950 as a prosthetic material. Its flexibility made it ideal for a number of applications which PTFE could not undertake.

The combined PTFE–silicon rubber shunt functioned even better, and PTFE was quickly relegated to just the arterial and venous tips, and to a bridge connector, the bulk of the shunt being silicone rubber (Fig. 14.3b). However, the arterial implant tended to need revision within 6–9 months, and the venous end even more frequently. Over the next few years the cannulae were improved in a number of ways and other variatons introduced such as the Ramirez straight shunt and the Buselmeier shunt, with two 'ears' for access. However, the life of all these shunts was generally never



(a)

(b)

Fig. 14.5 (a) Stanley Shaldon (b. 1931) who was not only a pioneer of acute and long-term dialysis in the United Kingdom, but the first to realize the full importance of patient independence in dialysis. (b) Shaldon in 1961 in his element—clinical dialysis.

more than several months in most patients without a need for some sort of revision or declotting, with or without the use of thrombolytic agents such as urokinase or streptokinase.

Nevertheless, long-term dialysis—thanks to cellulose membranes, thanks to heparin, thanks to PVC, thanks to PTFE, thanks to silicone rubber—was now possible. Other approaches were made to making repeated dialysis available, notably by Stanley Shaldon (b. 1931) (Fig. 14.5) at the Royal Free Hospital in London, by percutaneous puncture for acute renal failure [15–17] using the needle and wire technique introduced by the Swede Sven Ivar Seldinger in 1953. This method was then modified and used by Sergio Giovannetti in Pisa, Italy [18] for longer term dialysis.

It is worth pausing here to consider how all this new technology was received in the early 1960s, and this has been analysed in detail by Peitzman [19]. Although the picture of an instantaneous ecstatic welcome has been described with hindsight [10], at the time many expressed major doubts. His ex-mentor Malcolm Milne is alleged to have remarked, when he first saw the dismal effects on patients of early attempts at long-term dialysis: 'I wish now I'd pushed Scrib under a bus' [in 1958 when he was in London].

Certainly numerous physicians all over the world attempted, without Scribner's skills, commitment and attention to detail to perform long-term dialysis and failed miserably, the majority of them remaining silent about their failures. Others (reviewed in [19]) were more vocal about their disastrous outcomes. It took about 4–5 years before long-term haemodialysis was generally perceived as a treatment which could

be expected to produce reasonable results (see also Chapter 21) and the generally poor outlook for young dialysis patients even by the end of the 1960s deserves emphasis (see Chapter 16), even though anything was better than the universal death experienced by such patients hitherto.

The arteriovenous fistula

Then in 1966, when most of the nephrological world was struggling with a notable and universal lack of success to lengthen the survival of their PTFE–silicone rubber shunts, another sensational advance swept into the field and made external shunts obsolete almost overnight: the needling of a previously created subcutaneous arteriovenous fistula, described by New York physicians Michael Brescia and James Cimino (b. 1928), surgeon Keith Appel (Fig. 14.6) and resident Baruch Hurwich [20,21]. The idea arose from Cimino's experience as a phlebotomist in the Bellevue Hospital blood

(a) (b)

Fig. 14.6 Left, James Cimino; centre, Keith Appel; right, Michael Brescia, pioneers of the arteriovenous fistula for dialysis access (from [20]). Inset: Dr James Cimino in 1998 (courtesy Dr Cimino).

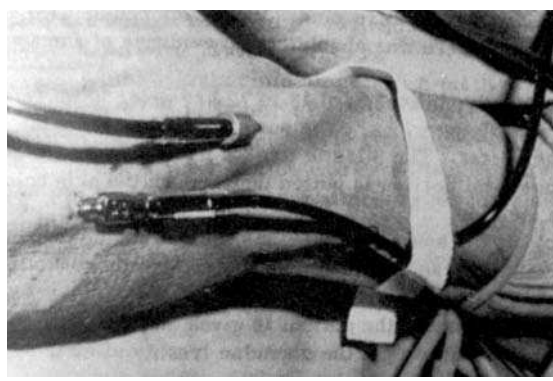


Fig. 14.7 An arteriovenous fistula for dialysis in use. This was the single most important advance in the practice of dialysis from 1960 to date. (From [20].)

bank whilst a medical student in New York [22], which led him and his resident Brescia to attempt and achieve venovenous dialysis using a simple occlusion cuff and wide-bore needles as early as 1961–1962 [23]. Because not all patients had veins of sufficient calibre, or were overloaded enough to provide adequate flow, the idea of enlarging the veins using a surgical arterial anastomosis arose (Fig. 14.7), and although this meant that a blood pump had to be used (unlike using the PTFE–silicone rubber shunt), its advantages for almost every patient were immediately obvious.

When this new idea was presented to the ASAIO meeting in April 1966, however, it had little impact—surprising in view of the fact that the shunt was clearly long-term dialysis' Achilles heel in every unit [22]. Nevertheless, the full publication in the *New England Journal of Medicine* [21] was accompanied by a laudatory editorial by Scribner, and the idea immediately spread. The following year (1967) self-needling by patients at home was reported by Shaldon [23], and the year after that the idea of using autologous saphenous vein to connect the artery and vein was tested and found successful [24]. Within a decade, almost every long-term patient was using an arteriovenous fistula to dialyse. Unlike all other major developments in dialysis, the arteriovenous fistula did not require new materials—only new ideas.

James Cimino's name is rightly known to every doctor, nurse and technologist involved in nephrology, and it is interesting to note he has published just six scientific and clinical papers other than on his eponymous fistula. One really good idea is enough for enduring fame. It is also worth speculating that had Scribner and Quinton never developed their PTFE–silicone rubber shunt—which was in retrospect only a 'half-way' technology which was useful for only a few years—long term dialysis would have been achieved anyway, sooner or later, using some sort of fistula.

The growth of dialysis units

Unlike dialysis for acutely ill patents in sudden renal failure, the 'patients' undergoing what rapidly came to be called 'regular' rather than 'intermittent' haemodialysis were reasonably well and lived at home, coming to the hospital only for their dialyses, in a largely outpatient 'salon of depuration for chemically unclean bodies' as Peitzman [19] has described it. This involved a number of patients coming and going, major consumption of disposable materials, and cyclical preparations for treatments: an altogether new form of medicine resembling a spa or gymnasium rather than a hospital ward.

In this novel setting Scribner's group in Seattle faced a sudden mass of problems which the new technology had opened up: medical and mechanical [26,27] as well as social and ethical [28–30]. On the technical side, because the hand-mixed dialysate tanks became breeding grounds for bacteria, at first refrigerated dialysis and then an open-pass system was adopted [12,26,27,31]: this necessitated large quantities of dialysate. Scribner approached the Department of Chemical Engineering in Seattle, and chemical engineer Albert L. Babb joined the team. Together they designed a proportionating pump system to blend concentrated dialysate salts and water using continuous flow, known initially as 'the monster', but then miniaturized it for individual use [26–28]. This was one of the early involvements of engineers in the design of dialysis systems: during the 1960s this became a feature of dialysis development, although as

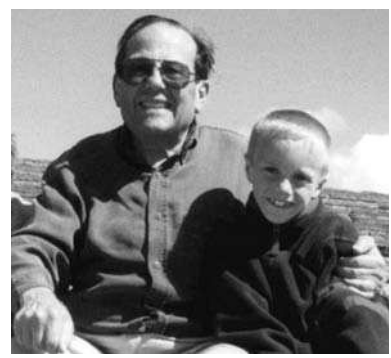
noted below the engineers remained constrained by the continued inability of the clinicians and biochemists to tell them what they should be trying to design for. Many of these proportionating machines are illustrated in Drukker's article [29].

Home haemodialysis

The development of the proportionating system came about because of the impossibility of dialysing all the patients who needed it in the unit. Self-dialysis by the patient was one answer, and almost simultaneously the idea of self-dialysis in the patient's own home as a means of making the treatment both cheaper and more widely available was developed independently at several sites. From his own account [30], Yukihiko Nosé (b. 1932) must be given credit for thinking of this idea first. His paper of 1961 which described a system involving a coil kidney that closely resembled the earlier system of von Garrelts in Sweden [32,33] and a domestic washing machine as a dialysate tank was published, however, only in Japanese, and was unknown to all in the West [34]. He recalls the negative reaction of Scribner, Merrill, Kolff and others when he tried to promote the idea in 1963 in the United States, after an abstract on the subject had been turned down for presentation at the ASAIO meeting that year [30]. However, 2 years later in discussion at the ASAIO meeting in 1965 he reported his early experiences [33], and this was the first those outside Japan (other than the reviewers of his 1963 abstract) knew of his efforts.

Obviously the idea was reconsidered in the United States, and independently in the United Kingdom, so that several groups began home dialysis almost simultaneously during 1964: in the United Kingdom Stanley Shaldon [34] (Fig. 14.8) using Kiil dialysers in the autumn, and in the United States not only by Scribner [35] who began

(a)



(b)

Fig. 14.8 (a) Medical student Robin Eady (b. 1940), who began dialysis in Seattle in 1963 and was one of Shaldon's first self-care patients the following year on his return to the United Kingdom, and then one of the earliest home dialysis patients in 1966. Today Professor Robin Eady MD FRCP has been on renal replacement therapy for almost 40 years, after many years on dialysis followed by a transplant in 1988, and is himself a distinguished clinician and researcher (see Chapter 22, ref. [29]). (b) Professor Eady today with his grandson.

his programme in the September, but also Merrill and his team [36] who used a twin-coil system starting in July.

Today it is difficult to appreciate what a radical move dialysis at home was. The idea of saving life by means of a machine had itself only barely become accepted a few years earlier, and now life was being prolonged indefinitely. Yet these 'mad dialysis doctors' were now sending their patients home, with a dozen ways in which they might accidentally kill themselves, and without any detailed prior examination—even in the litigation-minded United States—of the legal responsibilities and position. Scribner's beginnings in this field were understandably cautious: their first home dialysis patient was a trained nurse whose husband, an engineer, had built a machine for her [35], and Shaldon's first home dialysis patient was likewise a nurse with an engineer husband [34]. There was intense medical and press interest in the venture, particularly when Shaldon pointed to the increased self-esteem and sense of control which home dialysis patients acquired [37]—an important and ultimately influential article in the history of medicine as well as in nephrology.

As in so many other aspects of medicine, the new technology of dialysis forced the evolution of patterns of care which have since been exploited more widely. Dialysis was a technology which truly empowered patients in a ground-breaking way, and began a change in the face of Western medicine, altering the doctor–patient relationship in a fundamental way from a paternalistic relationship into a partnership. During the rest of the 1960s the proportion of patients doing dialysis at home increased steadily, fuelled by the charismatic advocacy of Scribner and Shaldon, although the majority of patients in all countries except the United Kingdom (see Chapter 21 and 22) continued to have in-centre dialysis. The fact that the great majority of patients in renal failure neither wanted nor were capable of sustaining home haemodialysis remained concealed for almost another decade (see Chapter 17).

The beginning of dialysis monitoring

To do haemodialysis at home meant that the safety of the dialysis procedure had to be improved. At the beginning of the 1960s, during haemodialysis patients potentially could be overheated, chilled, filled with air, bled in or out, dialysed against the wrong solution so their blood cells broke down, infected, or poisoned with too much calcium or a variety of agents which could get into the circuit, such as copper. A physician was present throughout the whole dialysis to ensure that none of this happened, or to take early action if it did. Under the pressure to do repeated large numbers of dialyses, even before home dialysis was contemplated, safety monitoring systems had to be devised. The earliest were on-line sensors to determine that the concentration and temperature of the dialysis fluid was appropriate. Then came air detectors to avoid air embolism. Without these simple measures dialysis at home would have been impossible even to contemplate. Thus a 'dialysis monitor' quickly evolved, designed for a single patient, standing sentinel by the patient's bed or chair—as they still do today, in a much more sophisticated and computerized form. These early 'monitors' not only blended the dialysis fluid from concentrated salt solution and processed water, as Scribner and Babb had introduced, but also measured the quality and temperature of the fluid and detected air in the circuit [38]. Even so, there was not uni-

versal agreement about adding this extra sophistication. Kolff remained of the opinion that self-dialysis could be kept simple and cheap, perhaps using a 'volksniere' (as Harry Lee in England called this approach) of hand-mixed dialysis fluid prepared from dry salts and raw tapwater in a tub and using a coil dialyser, with dialysis done during daylight hours rather than at night with the patient asleep. The many dangers of some raw tapwater were not yet evident (see Chapter 18) and the repetitive burdens of this simple but tedious approach were not popular with patients, who preferred a self-service cafeteria—or even better a restaurant—to cooking for themselves.

Hitherto all fluids for haemodialysis had been physiological fluids based on Sidney Ringer's original formulation of a century before, containing lactate and equilibrated with CO_2 to provide base to dialyse into the patient and correct the failure of hydrion excretion. On the basis of work by Gilbert Mudge and colleagues from 1949 that acetate could be metabolized to provide free bicarbonate, Charles Mion of Montpellier [39], visiting Seattle from France, showed in 1962–1963 that acetate could be used as a base for dialysis fluid. This was particularly important in allowing continuous and batch preparation of large volumes of dialysate. For 25 years acetate was the standard, until its toxicity for some patients became evident, and automated bicarbonate delivery systems became available. The use of acetate permitted the creation of the integrated dialysis systems involving both dialysate production and monitoring facilities just discussed, such as those of the Sweden Freezer Company and the Drake–Willock Corporation which were developed in association with the Seattle unit. Soon many similar machines were on the market in many countries [37].

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Chapter 15

New materials and methods II: long-term peritoneal dialysis becomes possible

Meanwhile, a similar but less publicized revolution occurred in the field of peritoneal dialysis. However, even though becoming well established as a treatment for acute renal failure during the 1960s, it would take 20 years more before a viable alternative to really long-term haemodialysis became available.

The beginnings of long-term peritoneal dialysis

Even so, it is worth remembering that the first long-term peritoneal dialysis patient, Mae Stewart, a 33-year-old black woman from San Francisco, started treatment before Clyde Shields and Harvey Gentry began haemodialysis in Seattle in March 1960, using a Murphy–Doolan catheter (see Fig. 11.16c) at the beginning of 1960.

In late 1959, Mrs Stewart had attended Dr Richard F. Ruben (see Fig. 11.16b) at the Mt Zion Hospital in San Francisco, who found she had preterminal uraemia with small kidneys. Dr Ruben had worked with Paul Doolan at the US Navy Hospital in Oakland as a resident, and admitted her there, where peritoneal dialysis was begun with improvement in her clinical condition; the catheter was left in place and clamped off, but she deteriorated over the next 2 weeks. A further dialysis was undertaken and then another, and another. Each time her plasma creatinine reached 20 mg/dL (2100 μmol/L) she was dialysed down to a level of about 13 mg/dlL(1500 μmol). Long-term peritoneal dialysis for irreversible renal failure had begun, almost by accident. After 3 months and 12 dialyses a new catheter was required, inserted and used. However, she developed pericarditis in April 1960, refused further treatment and died on 4 June 1960 after 6 months on dialysis. Drukker [1] (from whom the above account is taken, as told by Dr Doolan and Dr Ruben to him), notes that Dr Ruben's paper describing all this was turned down for publication, because it was only a single case report, and survival of the patient was short! Paul Doolan says that John Merrill was the reviewer, and gave an adverse review because he feared the spread of inadequately performed peritoneal dialysis as a result of the paper.

Meanwhile Fred Boen (b. 1927) (Fig. 15.1a) had joined the Seattle group from Amsterdam at Scribner's invitation, and when one of their early haemodialysis patients, a 28-year-old man, ran out of vascular access a plastic conduit was implanted

(a)

(b)

(c)

Fig. 15.1 Pioneers of peritoneal dialysis in the 1960s. (a) T.S. (Fred) Boen (b. 1927), who studied peritoneal dialysis from 1951 to 1959 in Amsterdam and from 1959 to 1965 in Seattle, and played a major role in introducing long-term intermittent peritoneal dialysis (courtesy Dr Boen). (b) Henry Tenckhoff (b. 1930) of Freiburg and Seattle, who made many contributions to peritoneal dialysis, espcially its chronic use (courtesy Dr Tenckhoff). (c) Urologist Harold McDonald (1933–1991) of Downstate Medical Center, NY. McDonald was one of the last surgeons to innovate in the dialysis field, and designed several peritoneal catheters for acute and chronic use during the 1960s as well as a machine for single patient use, and was an author on numerous influential papers including one on 'dry weight' in haemodialysis. (From McBride [14].)

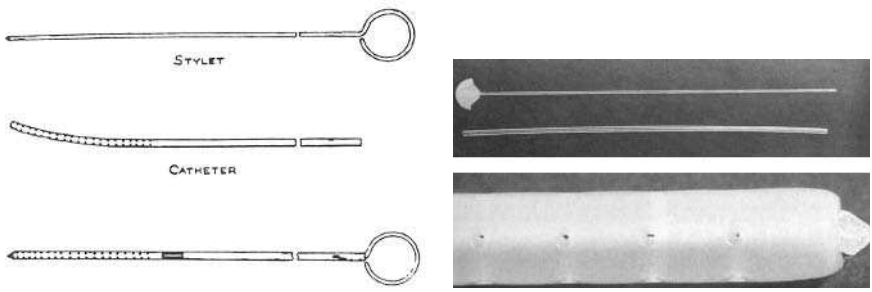
in April 1960 to allow repeated catheter insertion. After 4 months' successful dialysis, infections developed around the cannula and adhesions developed; he died after 6 months on dialysis. Boen began a long-term peritoneal dialysis programme, the first in the world, using Teflon® and silicon rubber tubes for access [2,3]. John Merrill, involved as always in any aspect of renal disease, also tried implanting a plastic catheter for long-term use, and treated five patients in this way from 1961 [4]. By 1964, Boen and his new colleague Henry Tenckhoff (b. 1930) (Fig. 15.1b) were ready to try home peritoneal dialysis, now using multiple punctures for access as they had become disillusioned by the poor results using conduits and indwelling catheters. Tenckhoff [5] had trained in Freiburg in Germany and spent time in Boston, some of it with John Merrill, during the 1950s. Returning briefly to Germany, he replaced Charles Mion as fellow in the peritoneal dialysis programme of Scribner's unit in 1963 when the latter returned to France, whilst Tenckhoff remained in Seattle.

New catheters and cycling machines

Boen and Tenckhoff used to begin with a catheter described by urologist Harold McDonald (Fig. 15.1c) of Downstate Medical Center, NY [6], and then used the Weston and Roberts stylet model (see below) designed for acute use. They used also the first of several automatic cycling machines designed and built by Tenckhoff with help from George Shillipetar, to supply the dialysate using 20 L and then 45 L carboys to hold the large volumes needed [7]. This allowed greater sterility, with an unbroken connection throughout the dialysis, but were cumbersome and heavy to transport to the patients' homes; although later the introduction of means of producing water in the home by stills or (in 1969) reverse osmosis systems [8] obviated this, using a process similar to that for desalinating seawater. The procedure was time-consuming, and ultimately unsuccessful compared with haemodialysis, since all their patients developed peritoneal adhesions following repeated episodes of infection, and dialysis became more and more difficult and ineffective; most died within a short time or had to be transferred to haemodialysis.

Thus it became apparent that, whilst it had become an excellent treatment for acute renal failure, peritoneal dialysis in its then current form was suitable only for holding patients for short periods whilst they awaited haemodialysis, or for a renal transplant [9].

The key was clearly easy infection-free access to the peritoneum, which remained a problem even for dialysis of limited duration. In 1964, two major advances were made, whose simplicity reflects the elegance of all good solutions. First Marty Roberts, a research chemist, visited Dr Ray Weston at the Cedars–Sinai Hospital in Los Angeles, where Maxwell's team were based, and saw the insertion of a rigid peritoneal catheter. A trocar necessarily larger than the catheter was used which—as always—when the trocar was withdrawn resulted in a small gap between the catheter and the walls of the trocar wound, through which bacteria would sooner or later penetrate. Roberts made the simple but brilliant suggestion that rather than using a trocar, a sharp stylet should run down the inside of the catheter, so that when withdrawn, the catheter would fit snugly into the hole made in the abdominal wall thus limiting bacterial access (Fig. 15.2) [10]. This became, and remains, the standard

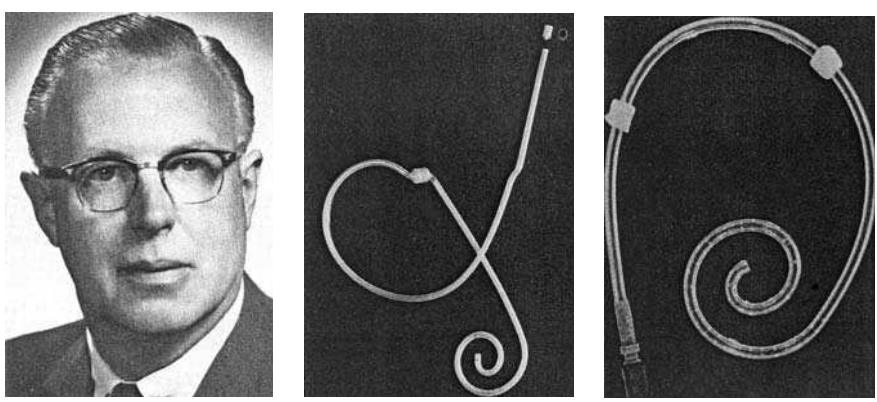


(a) (b)

Fig. 15.2 The stylet peritoneal access catheter of Weston and Roberts. (From [10], with permission. See Permissions.)

method for inserting a rigid peritoneal dialysis catheter, and was made available commercially through McGaw Laboratories as the Trocath®.

However, the rigid nylon or polyvinyl chloride catheter used for acute punctures of the abdomen was not the solution for long-term peritoneal dialysis, as Boen and his colleagues soon found. Something new was needed. As so often throughout this story, new materials were the crucial factor. As with access for haemodialysis, the vital advance was the availability of silicone rubber tubing from 1960 onwards, as discussed above. Russell Palmer (1905–1999) of Vancouver (Fig. 15.3a), who was one of the first to use haemodialysis in Canada in the 1940s (see Chapter 11), recognized the potential of his material for an intraperitoneal catheter. He asked Wayne Quinton in nearby Seattle, knowing of his experience of silicone rubber tubing for arteriovenous shunts, to design and make one, which Quinton did in an afternoon. The result was



(a) (b) (c)

Fig. 15.3 (a) Russell Palmer (1905–2000) of Vancouver. (b) The implantable Palmer–Quinton catheter of 1964 for long-term use. Reproduced with permission. See Permissions. (c) The Tenckhoff modification of Palmer's catheter. (Courtesy Dr Palmer, from [11].)

an implantable silicone rubber catheter with multiple side holes and a large end hole, with a single flange near the beginning to anchor it, to be embedded within the abdominal wall, leaving the catheter free in the peritoneum (Fig. 15.3b) [11,12]. This was reported in the *Lancet* a few months before Weston and Roberts' paper in the same journal. A similar approach was made by Gutch in Nebraska [13] and by Harold McDonald (Fig. 15.1c) [14] in New York, who introduced the idea of a rough Dacron® cuff on the catheter to anchor it. McDonald has received insufficient attention for his major role in the 1960s in the beginnings of long-term peritoneal dialysis. Born and trained in Atlanta, GA, he worked in the south and then in Boston in John Merrill's unit and developed his interest in Michigan before going to New York in 1964. His first appearance in these pages is with Merrill in the design of a disposable insert for the MacNeill–Collins dialyser (see Chapter 12, ref. [32]). He then developed, in Michigan, as noted above, the trocar method of peritoneal dialysis insertion [6] and there began home peritoneal dialysis in 1962, as well as pioneering the cuffed catheter [14]. Finally (see below and ref. [19]), he developed and used an early cycling machine for peritoneal dialysis.

However, it was the later modification of the Palmer–Quinton model by Tenckhoff [15] which produced the durable catheter still in use today, 35 years later. Tenckhoff found that the single cuff of the Palmer and McDonald models did not prevent entry of bacteria and consequent peritonitis, and used instead two separate subcutaneous cuffs made of Dacron® to anchor the catheter (Fig. 15.3c). This soft catheter could be introduced by trocar using an internal stylet just as with the rigid model. Although this type of catheter has ever since been commonly called a 'Tenckhoff' catheter, this is unkind to Palmer, who first thought of using silastic, and to McDonald who introduced the attachment of a cuff; to be fair it should be called at least the Palmer–Tenckhoff catheter; but then eponomy is almost never fair to innovators.

Throughout the 1960s several groups, starting with Boen in 1960 [2,3] and Merrill in 1961 [4], tried to provide access to the peritoneum through some form of button or conduit implanted into the peritoneal wall (sometimes called 'belly buttons'), through which a catheter could be repeatedly inserted, and which was self-closing in the meantime. Blumenkrantz [16] and Palmer [17] review these various devices, now only of historical interest. Kevin Barry and colleagues inserted their indwelling device though a trocar in 1963, whilst Ray Weston's of the same year had wings to keep it in place so it could be removed without surgery. Jacob and Deane's prosthesis kept the channel open, but was removed before use. Others tried the different approach of a subcutanous device which would prevent the frequent infections seen with these models, which could be needled for use; but problems with flow prevented their widespread use.

The 1960s saw many groups try to develop further cycling machines to perform automatic peritoneal dialysis for individual use in both the United States (McDonald, Kevin Barry, Keith Curtis and Norman Lasker) [16–20] and in Europe (Antonio Vercellone in Italy and Neter Mallick in Manchester, England) [21–23], following the early lead of Tenckhoff's group in Seattle. Some of the newer machines simply involved fluid circuits augmented with pumps and switches only, but others also prepared the dialysis solution from concentrate and water. One must recall that a major

difference of peritoneal dialysis from haemodialysis is that the dialysate instilled into the abdomen must be and must remain sterile, so the water had to be so as well. Usually water for dialysis was generated by distilling or deionization, later by reverse osmosis. In many ways this machine-driven peritoneal dialysis abandoned one of the technique's principal features, which had made the Grollman–Maxwell approach (see Chapter 11) so attractive around the world: simplicity. However, efforts to automate the technique have continued up to today, and in the past decade have reached wide application.

Clinical use of peritoneal dialysis in the 1960s

Even to almost the end of the 1970s, intermittent peritoneal dialysis was a minority interest for the treatment of chronic irreversible renal failure, and given the major unsolved problems with maintaining infection-free access this is not surprising. The number of patients being maintained on intermittent long-term dialysis was tiny, and even in Seattle in 1970 there were only 11 patients maintained using long-term peritoneal dialysis [24]. On the other side of the Atlantic, only one or two enthusiastic units, two of which were run by physicians who had trained in Seattle (Charles Mion in Montpelier in France and Fred Boen, back now in Amsterdam), were using the technique. Thus in 1970, only 102 patients were maintained on long-term intermittent peritoneal dialysis in the whole of Europe, out of a total of 5133 on some form of dialysis (2%).

Peritoneal dialysis for acute renal failure in the 1960s

Despite its minimal use for long-term patients, peritoneal dialysis as simplified by Grollman and Maxwell, or other similar systems, enjoyed great popularity throughout the world for the treatment of acute potentially reversible renal failure throughout the decade. Unlike long-term dialysis, there are no figures to tell us how many physicians used peritoneal dialysis and how many haemodialysis for acute renal failure (or indeed how many patients were treated overall for acute renal failure, with or without dialysis), but a personal recollection is that the majority of units in the United Kingdom were using peritoneal dialysis at least some of the time [25]. The number of papers from all over the world at that time describing its use suggest the same was true almost everywhere. This may have been in part because—as in the United Kingdom—in most renal units haemodialysis facilities were now crowded out and overwhelmed by patients receiving regular haemodialysis. For example, our unit at Guy's Hospital employed peritoneal dialysis almost exclusively on more than 100 patients with acute renal failure in the 3 years from 1965 to 1967, including very ill, hypercatabolic patients [26]. However, these required continuous dialysis for days at a time, and in retrospect may have been better treated with haemodialysis—although the mortality remained just as high in such patients, whatever the treatment [27], and sadly still had not been reduced by the end of the century whatever the treatment used [28] (see Chapter 16).

It is interesting, given this major problem of management, that there was remarkably little debate [29], and no controlled studies, comparing peritoneal dialysis and haemodialysis in the treatment of acute renal failure either then or since. For two

decades, the treatments were used side by side, some favoured more by one unit, some more by another unit, according to local preference and facilities, until ultrafiltration methods entered the scene as an alternative and eventually became the dominant form of treatment (see Chapter 17). Peritoneal dialysis has remained up to the present day the preferred treatment for smaller children and infants, however.

As well as attempts to automate the procedure, efforts were made also to regenerate the dialysate, as was later to happen for haemodialysis. This was achieved by hybrid systems involving the recirculation of the used dialysate into an extracorporeal dialyser [30,31] as illustrated and described by Drukker [1], but the complexity of such systems ensured they were not widely adopted or used for long.

Two interesting and important observations made in peritoneal dialysis patients during the mid 1960s had major implications for dialysis as a whole in subsequent years. The first was by Lee Henderson in 1965 [32,33] that urea transfer was greater when ultrafiltration was being performed using dialysis with hypertonic glucose; that is, the volume of fluid extracted in bulk by the osmotic agent contained significant amounts of urea and other metabolites, in addition to that dialysed by diffusion. This 'convective' transport Henderson related back to attempts to ultrafilter plasma for their removal by Malinow and Korzon in 1946 and their predecessors Brull and Geiger in the 1920s (discussed in Chapter 17) which set him thinking, and led to the development of ultrafiltration as a treatment of uraemia.

The other was the observation by Scribner, as ever the astute and careful clinician, that patients using peritoneal dialysis were often fitter clinically despite their urea and creatinine concentrations being higher than those receiving haemodialysis. Also, patients on peritoneal dialysis suffered less from neuropathy, one of the main problems in dialysis patients during the 1960s. This led him in discussion at the American Society of Artifical Internal Organs in 1965 [34] to begin speculation as to whether the greater permeability of the peritoneal membrane to molecules larger than urea and similar solutes might play a role, and to generate what came to be called the 'middle molecule hypothesis' (see Chapter 17).

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26. In the absence of hard data this comment is based only on recollections of conversations with colleagues at the time. Certainly in the UK peritoneal dialysis took over the major load of acute renal failure patients in some units, except those with intra-abdominal problems either already present, or created surgically—although it was often technically possible to treat even such patients using the peritoneum for dialysis. However, most physicians preferred to treat their most ill, septic and catabolic patients with haemodialysis (see Cameron JS. Growing points in renal disease: acute renal failure. *Br Med J* 1966; **2**: 811–13, and the letters of Kennedy AC, Luke RG, Briggs JD. Peritoneal dialysis in renal failure. *Lancet* 1967; **i**: 1328–9; Flynn CT. Peritoneal dialysis in hypercatabolic acute renal

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Chapter 16

Dialysis patients in the 1960s and 1970s: old and new complications

Long-term dialysis patients in the 1960s and 1970s

By 1965, about 100 units worldwide had started long-term dialysis programmes, so that in September of that year 168 individuals were on dialysis in Europe (probably all on haemodialysis), and maybe somewhat more in the United States, a handful of whom were receiving peritoneal dialysis. By the end of the decade in 1970 their number had multiplied to over 5000, still the overwhelming majority receiving haemodialysis. A further 10 years saw the world total of people on dialysis leap dramatically to about 140 000 in 1980, and a significant and rising proportion were receiving peritoneal dialysis in the form of CAPD (see Chapter 19). Who were these patients?

To begin with, although no official rules or guidelines existed as to who was physically 'suitable' for dialysis, a rather narrow spectrum of individuals were referred to and entered this new treatment. In Seattle the 'suitable' patient was defined as an emotionally stable, co-operative patient without severe hypertension, between 20 and 45 years of age, who lived within reasonable distance of the dialysis unit and preferably had some residual renal function [1,2]. They should also have a job, be studying or be looking after a family. Many other units in the United States and elsewhere followed their lead, even though there was lively, important and influential debate on the idea and process of selection of patients for life-saving treatment [3]. In 1966 the topic was discussed in a Ciba Foundation symposium [4,5], and as late as 1967, in the *British Medical Journal* a discussion on the issues of patient selection for dialysis was published [6]. The acceptance on the part of all the participants in this discussion that the selection of only a few patients for treatment should be the norm is revealing. The idea of a panel of 'judges' on the Seattle model did not receive any support: 'I can see no justification for delegating this responsibility to lay persons' wrote Ralph Shackman, the surgeon in charge of the transplant programme at the Hammersmith Hospital in London [5]. During the 1970s the range of patients treated widened and discussion of the selection of patients waned, with little if any structured debate on this crucial issue even though the selection of patients still took place in most countries. This topic is considered further in Chapter 21.

Patients with *systemic disease* were excluded almost completely from long-term dialysis treatment during the 1960s, which was particularly hard on diabetics, who suffered renal failure as part of their condition with some frequency, perhaps 40% of young insulin-requiring diabetics at that time entering renal failure. The extraordinary story of diabetes and chronic renal failure is told in detail in Chapter 20 and

is a paradigm of the management of renal failure in a setting of systemic disease. In patients with systemic lupus, as an example of rarer systemic diseases, after a cautious start during the 1970s following the first report of Norman Coplon and his colleagues at Stanford, CA in 1973 [6,7] it became evident during the 1980s (but after some initial concern [8]) that in general they survived as well as their peers with only renal failure to contend with. However, some rare systemic diseases rapidly acquired a sinister reputation both on dialysis and even after renal transplantation, such as oxalosis because of fatal involvement of other organs [9]. In 1984 following the suggestion of Richard Watts, combined renal and hepatic transplantation was performed for oxalosis by (Sir) Roy Calne and his colleagues in Cambridge, England and this has become standard treatment at least in Europe. Patients known to have any form of malignancy were simply never treated in the period up to 1980.

The middle-aged, elderly and children were almost never dialysed long term in the first half of the 1960s. The first preadolescent, however, was treated in Seattle starting in October 1962 at the age of 14 years [10]. Throughout the 1960s a cautious start was made to treating older children in chronic renal failure, usually with the intention of an early renal transplant, often from a parent. This slow start was prompted by strong fears that growth failure would persist and that development, both physical and psychological as well as social, would be inhibited [11]. However, cases treated remained very few. Our own paediatric programme started with a 10-year-old girl dialysed from October 1968 [12], and at about the same time units in Los Angeles [13] and Paris [14] started treatment of significant numbers of children. Almost all patients were initially between 10 and 14 years of age, with an occasional exception [15] and a series of younger children reported from San Francisco in 1970 [16], where long-term dialysis in children had begun very early in the 1960s but only as a prelude to transplantation. Publications from these pioneers persuaded the community that this was a treatment here to stay, even if it presented many unknown possibilities and major technical and psychological problems and by the end of 1971, 174 children were on dialysis in Europe. To begin with shunts were used exclusively, but by 1970 fistulae were in use in children [17], including in the home, although home haemodialysis was little practised in children [12], only 19 being on home dialysis in the European prevalent cohort of 1971.

From 1971, separate paediatric reports were published annually by the European Dialysis and Transplant Society (EDTA) in their proceedings (from 1986 in *Nephrology Dialysis Transplantation*) and these form a valuable documentation of the growth of treatments for end-stage renal failure in children in Europe. During the 1970s the treatment of end-stage renal failure in children became established as a routine, at least for children over the age of 5 years [11], with numbers rising from 174 to over a 1000 during the decade, and a need for 3–4 children per million total population per year to be treated was established. Statural growth was identified very early as the crucial problem of many technical aspects in which children differed from adults, and much attention was devoted to optimizing it using diet and good dialysis, until in the 1990s recombinant human growth hormone became available as well.

In the United States, from 1972 onwards, children were covered in the same way as adults and facilities expanded steadily, if not in a co-ordinated fashion. In the United

Kingdom, in 1974 the British Association of Paediatric Nephrology—a rather grand name for the mere dozen or so paediatric nephrologists caring for children in renal failure at that time (of which I was one)—produced detailed recommendations for a national service for the treatment of childhood renal failure [18]. Although this plan was accepted by government, the process was bogged down in administration and facilities lagged, with only a popular campaign on television and in the public press resulting in partial implementation of the plan by the end of the 1970s [19]. In most countries, by the 1980s even infants were receiving dialysis, usually by the peritoneal route, although transplantation was (and still is) viewed as the ultimate desired outcome.

The 'greying' of the dialysis population was the most obvious change in this group during the period 1965–1980 and has continued since (see Chapter 22); the average age rose from 39 years in 1970 to 54 years in 1980. Although autopsy and death certificate data were available even before long-term dialysis started, suggesting that renal failure was much more common in the elderly than in the young, these were generally ignored and renal failure in young patients arising predominantly from glomerulonephritis and 'pyelonephritis' received the most attention and treatment.

Complications of patients on long term dialysis from uraemia and other causes

It was no surprise that the introduction of long-term dialysis led to a surge in the frequency of the complications of uraemia in patients 'frozen' in a uraemic state by prolonged repetitive dialysis, which presented an immediate and complex challenge to physicians looking after these patients on dialysis treatment. To begin with these were the well-recognized secondary effects, described so well by George Schreiner and Jack Maher in their comprehensive book of 1961, written just as dialysis for chronic renal failure began and still well worth reading today [20], but also the complications and effects of the dialysis procedure itself [21].

Anaemia

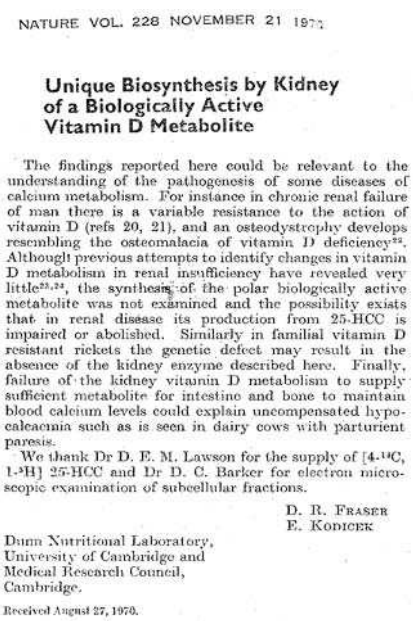
Severe anaemia, described 140 years previously by Robert Christison [22,23], was noted to be most severe in those patients submitted to nephrectomy [24,25], often for another complication, severe hypertension; whilst some fortunate patients with polycystic kidneys suffered little or not at all from anaemia. Although deficiency of erythropoietin was clearly the major factor in the anaemia of uraemic dialysed patients [26,27], the role of blood loss in the dialyser and blood sampling [28], as well as iron deficiency [24,28] became evident early. Transfusions were noted to be even more temporary in raising the haemoglobin concentration than usual, confirmed by a shortened half-life for the infused cells, and the resultant iron overload emerged as a growing problem. A dichotomy emerged during the early years as to how the anaemia should be managed. In the United Kingdom and in Seattle, patients were given iron, but were not transfused, their haemoglobin concentrations remaining about 7 g/dL. In contrast, in many European and other American dialysis units, regular transfusions were given. The vigorous correspondence which followed the publication of the paper

by Charles VanYpersele and Stragier [25] on the subject in the *Lancet* at that time illustrates these conflicting attitudes. Anaemia remained a major obstacle to the success of dialysis, and remained also resistant to treatment, despite some success with testosterone treatment [29,30] and later in the 1970s with anabolic steroids.

The evolution of knowledge on the genesis of the anaemia of renal failure, and its successful treatment with erythropoietin beginning in 1987 is told in Chapter 20.

Hypertension

Scribner had established in his first two patients that even severe hypertension could be controlled by ultrafiltration, and with characteristic perspicacity had emphasized the crucial role of volume in its genesis [1], thus confirming the predictions of Ludwig Traube from 1856 [31]. Studies of exchangeable sodium and volume were made early after the introduction of long-term haemodialysis [32], and the concept of the attainment of a 'dry weight' was given this enduring name in 1967 by Eli Friedman, Harold McDonald and their colleagues [33,34]. This was a body weight at which reasonable blood pressure control could be expected in most individuals, and patients were 'titrated' towards this by successive ultrafiltration [35]. The few hypotensive agents



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Unique Biosynthesis by Kidney of a Biologically Active Vitamin D Metabolite

The findings reported here could be relevant to the understanding of the pathogenesis of some diseases of calcium metabolism. For instance in chronic renal failure of man there is a variable resistance to the action of vitamin D (refs 20, 21), and an osteodystrophy develops resembling the osteomalacia of vitamin D deficiency[22]. Although previous attempts to identify changes in vitamin D metabolism in renal insufficiency have revealed very little[23,24], the synthesis of the polar biologically active metabolite was not examined and the possibility exists that in renal disease its production from 25-HCC is impaired or abolished. Similarly in familial vitamin D resistant rickets the genetic defect may result in the absence of the kidney enzyme described here. Finally, failure of the kidney vitamin D metabolism to supply sufficient metabolite for intestine and bone to maintain blood calcium levels could explain uncompensated hypocalcaemia such as is seen in dairy cows with parturient paresis.

We thank Dr D. E. M. Lawson for the supply of [4-^{14}C, 1-^{3}H] 25-HCC and Dr D. C. Barker for electron microscopic examination of subcellular fractions.

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(a) (b)

Fig. 16.1 (a) Treatment of severe hypertension, 1968 style. Note the choice of hypotensive agents available, and the effect of bilateral nephrectomy. (From Vertes *et al*. [35] with permission.) (b) A portion of the key paper from Fraser and Kodicek [52] in Cambridge, England which described how vitamin D was activated in the kidney and made effective treatment of the bone disease of renal failure possible.

available in the 1960s were relatively ineffective in patients on dialysis, and even worse led to severe hypotension during and after the procedure. Occasional patients with intractable hypertension worsened during dialysis and with extremely high plasma concentrations of renin had both kidneys removed to take away their source of renin, with dramatic relief (Fig. 16.1a). The first of such patients was treated in Kolff's unit in Cleveland in 1963 [36] and many others followed rapidly [37,38]. All these subjects, however, suffered as a result appalling anaemia, and this was early evidence that endogenous erythropoietin was removed almost completely as well as the renin. For a further decade, until the introduction of the first angiotensin-converting enzyme inhibitor, captopril, in 1978, this was the only route by which such patients could be managed.

Thus by the end of the 1960s most patients on dialysis were maintained normotensive using water and sodium restriction together with a gradual reduction in extracellular volume using long, slow dialysis sessions. Then, rather abruptly during the 1970s, came the change away from the long, slow dialysis of the 1960s discussed in the next chapter, with the result that blood pressure control became much more difficult using the short dialysis sessions now in vogue. Units which previously had no, or only a few, patients requiring hypotensive agents to control their blood pressure now found themselves with the majority of their patients taking some sort of hypotensive agent. Restriction of salt intake was regularly advised but often ignored, to the patients' detriment.

Cardiovascular disease

Locked to the problem of poor control of hypertension was that of cardiovascular disease in general. From 1965 onwards successive annual reports of the EDTA were the first warning that cardiovascular disease was the predominant cause of death, but at that time the average age of patients on dialysis was low (39 years in the United States in 1969) and it took some time for the true extent of this modern 'epidemic' to reach consciousness. By 1973 vascular disease was noted to account for about half of 4011 deaths of patients on dialysis in Europe [39]; the early data from Europe were followed by similar evidence from the United States dialysis registry in 1971 [40], and finally the landmark paper of Lindner and colleagues from Scribner's unit in 1974 brought the problem to centre stage [41] where it has remained ever since.

There were obvious risk factors for vascular disease in the dialysis population, of which hypertension was the most obvious, along with anaemia and high plasma phosphate concentrations, and including, of course, smoking to which the dialysis population is as prone as the rest of the population. At that time there were almost no diabetics receiving dialysis (see Chapter 20). The hyperlipidaemia of dialysis patients was studied and described during the 1960s, predominantly by the group of Bagdade [42], and was found to consist predominantly of hypertriglyceridaemia. Today, vascular disease is the main cause of death in almost all age ranges of the dialysis population [43,44] and this most important topic is discussed further in Chapter 22.

Gradually it became evident also that the uraemic heart underwent fibrosis and loss of capillary circulation, and that left ventricular hypertrophy, which a majority of dialysis subjects already had when they started or acquired later, was a powerful predictor of adverse cardiovascular events. The major role of anaemia in producing this

hypertrophy, independently of high blood pressure, has only become evident within the past two decades and is now the subject of much discussion.

Bone disease

A form of bone disease known as *renal osteodystrophy* had been known to appear in chronic uraemia since the nineteenth century [45–47]. Meanwhile the nutritional origin of rickets had been suggested by Gowland Hopkins in 1906 and culminated in the identification of pure vitamin D_3 by Askew and colleagues in 1930 [48]. In parallel, after the description of osteitis fibrosa cystica by Engel in 1864, the relation of this type of bone pathology to uraemic bone disease was established [46].

These bone diseases appeared in an accelerated form in the early patients on dialysis, who were subjected to high plasma phosphate concentrations for longer than patients dying of uraemia because of inadequate phosphate removal by even 'good' dialysis. This often led to dramatic *soft tissue calcifications (calciphylaxis)* [49] or to diffuse arterial calcification [50]. Attempts to limit plasma phosphate concentrations by better dialysis and aluminium-containing phosphate-binding agents were often unsuccessful, and in the 1960s rampant *hyperparathyroidism* was common, especially as no form of vitamin D effective in uraemics was available, and the true nature of the active vitamin D molecule was several years in the future. Ironically, one relatively active vitamin D preparation was already available (dihydrotachysterol [47]), but few renal physicians were aware of it by the 1960s, although it was (for example) in regular use in our own unit amongst others. Crude assays for immuno-reactive parathyroid hormone iPTH were only just becoming available at the close of the 1960s, so treatment was based on symptoms and radiological findings. The dire consequences of aluminium loading only became evident during the 1970s, when aluminium in dialysate was shown to be the cause of dysarthric progresssive dementia, associated in turn with a fracturing adynamic osteodystrophy in many patients (discussed in Chapter 18).

Then in 1968 Hector deLuca and colleagues at the College of Agricultural and Life Sciences in Wisconsin showed that the active form of vitamin D_3 was in fact a 25-dihydroxy derivative of the vitamin D molecule in the diet and was manufactured in the liver [51]. This paved the way for D.R. Fraser and E. Kodicek [52] in the Strangeways Laboratory in Cambridge, England to make the surprising discovery that active vitamin D required a further hydroxylation at the 1-position, and that this transformation occurred uniquely in the kidney. Later, the enzyme responsible was shown to be principally localized within the proximal renal tubular cells. The reason for the well-known resistance of patients with renal failure to simple vitamin D (cholecalciferol) was immediately evident to the authors [52] (Figure 16.1):

> in chronic renal failure of man there is a variable resistance to the action of vitamin D and an osteodystrophy develops … the possibility exists that in renal disease its [i.e. 1,25OHvitD] production from 25-HCC is impaired or lost. Similarly in familial vitamin D resistant rickets the genetic defect may result in an absence of the kidney enzyme described here.

Treatment with the fully active hormone became possible and was quickly realized with the synthesis of the 1,25 compound by deLuca's laboratory in 1972 [53].

However this synthesis was difficult, and both deLuca and Kodicek realized that if 1-α vitamin D could be given to renal failure patients, their normal livers would be capable of converting it to the active dihydroxy hormone. The synthesis of the 1-α compound proved much simpler, and was achieved by both groups [54], and was quickly proven to be effective clinically.

Once these powerful new agents became available, the treatment of renal bone disease was revolutionized during the 1970s and 1980s, much to the benefit of patients. However, phosphate control actually became much more difficult from 1980 onwards, not only because shorter hours of dialysis did not permit adequate removal of this rather large molecule, but also when the origin of aluminium-related dementia and bone disease became evident, the aluminium-containing phosphate-binding agents were shunned. The new vitamin D analogues appeared to be able to inhibit the development of hyperparathyroidism to some extent, but if it became independent of control, with adenoma formation within the parathyroid glands, then the antique treatment of surgery was the only recourse. It is curious and surprising that no really effective medical treatment for secondary—or even primary—hyperparathyroidism has yet entered the clinical field during the past half century, despite increasing knowledge of the regulation of parathyroid hormone (PTH) release and the identification of the calcium sensor.

Another change from the 1960s was the type of bone disease observed. To begin with the almost universal features seen in bone biopsies were the well-known appearances of hyperparathyroidism and osteomalacia. However, once techniques of assessing bone accretion improved, the presence of a third type of disordered bone was noted, in which there was little evidence of cellular activity either building or removing bone, and little or no bone accretion: *adynamic bone* [55]. To begin with in the 1970s most of the patients with this appearance were found to have toxic concentrations of aluminium, and the frank adynamic vitamin-D-resistant fracturing bone disease first defined in Newcastle, England (see Chapter 18) in the mid 1970s fell into this group. Whether adynamic bone observed in the absence of aluminium overload actually constitutes a 'disease', as it is so often labelled, remains unclear [56]. In the absence of aluminium, no convincing bone symptoms have been shown to result in those patients who have only adynamic bone without osteomalacia, even though their bone histology is clearly abnormal. Many of these patients are receiving chronic peritoneal dialysis, and some have associated the apparent upsurge of this appearance to some effect of dialysis treatment, as opposed to haemodialysis. The debate continues.

Malnutrition

During the whole of the 1960s, most patients were started on dialysis very late, having been for considerable periods on the very low protein [0.2–0.3 g/kg/24 h) diets popular at that time [57], often supplemented by an inadequate amount of energy. Even worse, in many units such diets were continued after beginning dialysis, in an attempt to limit the number of dialyses needed to twice or even once a week. The inevitable result was widespread and devastating malnutrition in the dialysis population. By the end of the 1960s, however, it was apparent already that *more* dialysis and an *increase* in protein intake towards normal was the better recipe, but it has become

clear that the uraemic state is an intrinsically catabolic one, as well as one in which appetite is usually limited.

With the advent of urea kinetic modelling in the 1980s (see Chapter 17), it became possible to calculate the protein catabolic rate from the rate of urea generation. This proved a powerful tool in thinking about nitrogen balance in patients on dialysis, but makes many assumptions and is, inevitably by its mathematical derivation, locked into the quantity of dialysis delivered as assessed by *Kt/V*.

Neuropathy

Almost all early patients starting dialysis in the 1960s were suffering from progressive, clinically evident peripheral neuropathy, sometimes of great severity [58,59] with burning feet and numb hands. Interestingly this was first described in 1873 by the founder of neurology, Jean Martin Charcot (1825–1893), whose nephrological work has received attention only recently [60]. Much attention was directed in using this as a means of assessing the adequacy of dialysis and the early dialysis schedules discussed in Chapter 14 were tailored to prevent—and it was hoped reverse—neuropathy [59]. An important series of papers were published by V.K. Nielsen in Denmark in the early 1970s which delineated the syndrome and its evolution under dialysis [61]. Although it remains present in subclinical form in most dialysis patients if nerve conduction studies are done, it has almost ceased to be a clinical problem.

As early as 1968, however, it was noted that most patients on dialysis suffered also from autonomic nervous dysfunction [62], which is not usually a problem although it is often supposed to contribute to cardiovascular instability in dialysis patients. The study of its pathogenesis, carried out intensively in the 1960s and 1970s, has waned with the decline in clinical importance of neuropathy. The search for neurotoxic 'middle molecules' which might be responsible is discussed in the next chapter, but in sum was without success.

The hepatitis plague: blood-borne viruses

As if all these problems were not enough, new and unexpected complications of dialysis also put in an early appearance. Within only a few years of the introduction of long-term dialysis, even by 1965, the frequency of clinical serum hepatitis [63] and abnormal liver function tests amongst patients on dialysis was evident, with deaths amongst staff as well as patients [64]. One of the earliest epidemics of hepatitis B in dialysis units was in Manchester, England in 1965 in which three of 14 affected staff died, and in the United States the pioneer units in Seattle and Downstate Hospital in Brooklyn both experienced hepatitis outbreaks during 1966. A survey conducted by the EDTA at the end of 1966 [65] revealed 65 centres doing dialysis in Europe, treating 480 current patients, having experienced 40 cases of hepatitis in 20 centres (27% of centres) with nine deaths (23%). Even worse, of 876 staff in contact with patients, 64 had been affected with three deaths and a number of other cases of hepatic coma with recovery.

Simple cross-infection measures were discussed and some were introduced, including the withholding of transfused blood as a treatment for anaemia, which was sus-

pected to be the main way of entry into the patients. However, at that time in most countries (including the United Kingdom) non-disposable metal needles and glass syringes were re-sterilized for use, providing another possible route of entry for the virus. The dialysis procedure involved regular access to the blood stream and the handling of blood, which was sent to a variety of laboratories for study. Finally, dialysis units were generally overcrowded and under intense pressures on time, staff and space to treat a mixture of acutely ill patients in acute renal failure and those on regular chronic dialysis, often in the same area: a recipe for an epidemic. Several major epidemics of hepatitis did sweep through dialysis units during the late 1960s, one in Edinburgh, Scotland being of particular severity, which led to the deaths of four of 12 affected staff in a single unit. There were fears that the acute services would be compromised or stopped, and the chronic dialysis facilities were inevitably compromised.

Hepatitis B turned out to be terrifyingly infective. I recollect two individuals who came into our dialysis unit during our epidemic of 1969–1970 involving 200 people all over the hospital [66], who observed but did not touch anything during an afternoon, yet both developed the disease—thus showing that it could spread not only by direct contact with blood but by airborne spread in the blood aerosols present in the atmosphere of dialysis units.

To begin with the responsible agent, presumed to be a virus by its behaviour, was unknown. In 1964 Baruch Blumberg [67] had described an antigen in blood, at first called the 'Australia' antigen after its discovery in an Australian aboriginal, that reacted with an unusual antibody in the serum of a mutiply transfused haemophiliac subject. Only when this 'new' antigen was linked in 1966 to a case of clinical hepatitis did its significance become clear. The fact that the majority of dialysis patients developed mild clinical disease and then became carriers explained the endemic and epidemic nature of the disease in dialysis units [68], and by 1969 the majority of cases were shown to carry the 'hepatitis-associated' or 'Australia' antigen, now implicated as the agent responsible for hepatitis B.

The timing of this discovery was fortunate, because it gave a powerful tool to those studying and aiming to prevent hepatitis by screening and isolation, including in dialysis units and of donated blood. Two reports were published from the Public Health Laboratory Service in the United Kingdom, the first [69] setting the scene in 1968–1969 including testing for hepatitis B from the beginning of 1969, since reagents to test for the Australia antigen became widely available at that time. In response to the worsening situation, a committee was convened under the chairmanship of (Lord) Max Rosenheim, which rapidly produced a report [70] describing 'good practice' for avoiding cross-infection in dialysis units that are still in use today. Similar initiatives were taken in the United States [71]. A further UK report in 1973 was able to say that the number of attacks was going down sharply [72], and another in 1976 that the battle was won [73], but damage had been done. In the eyes of the public and of colleagues within hospitals, dialysis units were 'dirty' places full of strange machines, where infection lurked and could break out at any time to affect adversely the work of the hospital as a whole. It may not entirely be coincidence that it was at this point that the expansion of dialysis services in the United Kingdom stopped (see Chapter 21). Patients who

were carriers of hepatitis B received poorer treatment for intercurrent illness and more slowly than other patients, often for the simple reason that they were in isolation; their mortality was higher than comparable patients. This was not unique to dialysis units: carriers of hepatitis B without renal failure found it difficult to get treatment promptly—or at all—in other areas of need within medicine [74].

It became apparent from population screening during the early 1970s that the virus was endemic in populations at large, with a variable carrier rate that was lowest in Northern Europe and highest in tropical countries and within Europe around the Mediterranean. Physicians in these countries could expect to take in a proportion of already infected patients, and both staff and patients continued to suffer from hepatitis in many countries. Staff usually recovered and then had lifelong immunity, but occasionally died of it during the acute attack. Patients, in contrast, who usually became carriers, might develop chronic liver disease in association with their persisting antigenaemia. New tests were developed, and a better description of the virus particle as a 42 nm coronavirus allowed more secure tracing.

Clearly immunization was a possible answer, and by 1979 a vaccine became available and could be used to immunize dialysis staff routinely [75], and also patients entering dialysis [76]. Intensive vaccination campaigns have largely removed the problem of hepatitis B, provided proper immunization and cross-infection protocols are adhered to. However, a continuing problem is that using available agents, a variable proportion of patients do not develop a useful antibody titre, presumably because of the immune depression induced by their uraemic state, even when manoeuvres to increase the immunogenicity of the vaccine are used.

Even in the 1960s, some patients were noted to have 'non-A, non-B' hepatitis in that they showed no sign of the hepatitis B antigen or antibody, the first hint of the existence of what came to be called *hepatitis C* [77]. This was not positively identified until 1990 [78], but the behaviour of these early patients with 'non-A non-B' hepatitis was disturbing, as most developed chronic liver disease. Although much less infectious than hepatitis B, so that 'good practice' is enough to prevent its spread [79], hepatitis C presents a major challenge to nephrology today, especially in transplantation.

Finally, even more hepatitis viruses have been identified during the1990s, including: the *delta agent*, hepatitis D; *hepatitis E* [80], a major cause of enterally transmitted non-A, non-B hepatitis; and yet other blood-borne viruses identified genomically—*hepatitis G* [81] and now the enigmatically named *transfusion-transmitted virus* (TTV). Although dialysis patients are carriers for these viruses more frequently than the general population, none of these appear as yet to be a clinical problem.

HIV infection

What *has* proved a problem is the worldwide epidemic of HIV infection evident since the first diagnosis of an AIDS-related syndrome in 1981 and the identification of the AIDS virus in 1984, raising the number of serious blood-borne viruses important in dialysis to at least three [82]. Again, good cross-infection practice in dialysis units can prevent its spread, but different parts of the world have varying rates of virus carriage in the general population from 0.1% to 20% or more, and inevitably therefore in the

intake of patients on to dialysis. A special problem are those patients, usually of African origin, who develop renal failure from AIDS-related nephropathy and require dialysis, described simultaneously from several units in the eastern United States in 1984 [83] as collapsing focal segmental glomerulosclerosis, although other patterns of both chronic and acute renal failure have emerged since [82]. The survival of such patients remains very poor at the time of writing, although the effect of combination antiviral therapy on this group of patients has not been evaluated fully as yet. As with hepatitis B carriers, discussed above, those unfortunate patients carrying the HIV virus are rarely given the same treatment as their fellow patients; for example, at the most obvious level, almost all transplant units are at best very reluctant to transplant HIV-positive patients, even when they remain symptomless, with donor kidneys in such short supply. The small number of data on their prognosis arises from patients transplanted accidentally or who acquired HIV post-transplant, or together with the donor organ. Here, also, the effect of modern combined antiviral treatments has yet to be evaluated.

The psychology of long-term dialysis

We cannot list the physical problems that early patients on long-term dialysis suffered without briefly remembering the psychological problems that they faced as well [84–86]. As noted in Chapter 1, there was no real precedent for their plight other than those patients maintained in 'iron lungs' for assisted ventilation, usually following poliomyelitis, and so no past experience from which they could draw support. The combination of relief at being alive, altered body image, change in lifestyle, dependence and loss of autonomy, anger, frustration, fear of the future, of connecting to the machine—and of the machine itself, with no clear idea of what would happen next—was a potent mix of problems, many of which still remain to confront patients today. The psychological damage this could bring was evident very early, as pioneer studies from Schreiner's unit in particular showed [83,84]. Later in the 1960s a number of groups published further studies on both the patients and the staff of dialysis units. These later studies drew attention to the peculiarly close relationship between patients and staff which developed in dialysis units. 'Psychonephrology' became the subject of an annual conference, and most units had much need of psychiatric advice. With the relatively young population of the 1960s and 1970s, stopping dialysis was not yet a problem; this topic is discussed below in Chapter 20.

Summing up long-term dialysis in the 1960s and 1970s

This rather grim list of complications makes long-term haemodialysis in the 1960s seem a trial rather than a success. Nevertheless, many patients were rehabilitated successfully and led useful and fruitful lives. Many were conscious of having been lucky to be on dialysis at all and struggled hard to continue their lives. By the end of 1969, long-term dialysis was established as an accepted medical treatment, despite all the medical, financial and political difficulties (see Chapters 21 and 22). The overall results were not as good as might have been hoped, however. In the annual EDTA reports of the late 1960s, annual mortality even amongst a young population ranged up to 40% per year and was still 20–30% in this relatively young group during the 1970s.

Finally, the small numbers of patients being treated even 10 years after the 1960 paper of Scribner *et al.* are worth bearing in mind. For example, in the United States even in 1970 [87] only 2660 patients (13/million population) were under treatment in 253 centres, 885 of whom were having treatment at home (33%); their average age was 39 years. The following 30 years were to see these figures leap 10-fold (see Tables 21.1 and 22.2) whilst home haemodialysis was marginalized and the mean age nearly doubled. In Europe in 1968, only 1281 patients were on dialysis and 114 units were operating; by 1970 these figures were 3150 and 380 [88] so that about 5500 patients were on dialysis treatment worldwide in that year. At this time, before the passage of entitlement law in the United States in 1972, it is interesting to see there were more patients on treatment by dialysis in Europe than in the United States—but this was rapidly reversed during the 1970s. In Japan in 1970, there were 182 dialysis stations available in an unknown number of units (probably about 10–15), and only 'about 500' patients were on dialysis—no accurate figures are available for a programme which had begun only about 1968 [89]. The huge expansions in dialysis programmes, particularly in Japan and the United States, were yet to come as the 1960s came to an end (see Table 22.1).

Patients going into acute renal failure

Patients with acute renal failure received much less attention in the published literature during the 1960s, probably because of the explosion of long-term dialysis and the huge interest in applying it. In many hard-pressed units their needs were sidelined to some extent by the pressing imperatives of the fledgling chronic dialysis programmes. Staff struggled to cope with the double demands of both the rapidly increasing regular work, and the intermittent intense demands of one or more extremely ill patients in acute renal failure, often being nursed in one of the new intensive care units, and thus another site of action for already overstretched dialysis staff to cover. Nevertheless there were many benefits for acute patients from the advent of regular intermittent dialysis. The advent of well-organized units doing many dialyses every week undoubtedly raised the standard of performance of both acute peritoneal and acute haemodialysis, and thus benefited patients with acute renal failure. The new shunts intended for long-term use again were a boon to those in acute renal failure, and reliable repeated access to the circulation for however long it was needed was no longer a problem, making frequent or even daily dialysis easy. Monitoring of dialysis rapidly became better under the impulse of the needs of the chronic patients, with an increase in safety. The idea of more frequent dialysis with a good dietary intake whenever possible was transferred from the management of the chronic patients. Haemodialyser design improved rapidly with the new improved higher performance flat-plate and coil dialysers, which in addition had a lower obligatory blood loss; physicians learned to be more careful about transfusions, especially with hepatitis lurking in the background.

What of the patients themselves who developed acute renal failure? The typical patient who was treated for acute renal failure in 1970 was very different from those of 1960 [90,91]. We do not know what the overall incidence of acute renal failure was in the 1950s or the 1960s, and whether it changed, since only from the mid 1970s were

any epidemiologic data gathered [92]. These surveys from the 1970s suggested that 30–60 patients per million total population per year might require treatment, whilst in an extensive European survey in 1983 [93] the EDTA found an average figure at the lower limit of this estimate. However, only units also performing long-term dialysis were questioned, so this number must be an underestimate. Therefore these data suggest that in countries such as Britain, France and Italy about 2500 patients per year with acute renal failure requiring dialysis could be expected, and in the United States perhaps fourfold more: 10 000 per year.

New causes of acute renal failure appeared, such as from antibiotics and other drugs toxic to the kidney, especially when the kidney was the only route for their removal from the body and accumulation became all the more likely as these failed. On the positive side, mismatched transfusions became rare, new soluble sulphonamides were introduced, septic abortions became less common, and all pregnancy-related acute renal failure declined in numbers and almost disappeared during the 1970s in developed countries. Mercury disappeared as a cause of renal damage. Urologists learned to use isotonic fluids for irrigation of the prostatic bed during prostatectomies, and this cause of haemolysis all but disappeared, whilst cardiac surgeons doubled the rate of perfusion during cardiac bypass operations in the early 1970s so that far fewer suffered renal problems even after prolonged bypass. Better surgical management of pre- and postoperative septic and electrolyte problems—often with advice from the staff of the new renal units—meant fewer collapsed patients. Lessons learned in the Korean and Vietnam wars led to better resuscitation of civilian casualties.

Paradoxically, as a result of all this progress, those patients who still managed to go into renal failure from accidental or surgical trauma, or intrinsic medical renal conditions, in the 1970s and 1980s formed an even more seriously ill cohort than those previously treated, and overall mortality did not fall: in many units it even rose (Fig. 16.2). Perhaps this was at least in part because the patients needing, and receiving, treatment were progressively older. John Turney and his colleagues [91] in

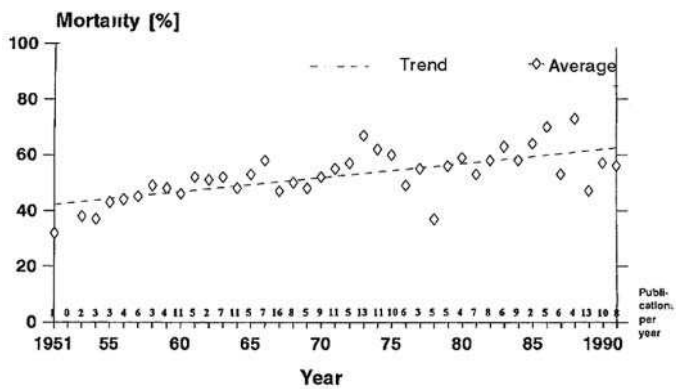

Fig. 16.2 The averaged survival of 32 996 patients with acute renal failure described in 258 publications over 40 years. (From Sieberth [94].)

their unique survey of patients treated for acute renal failure in Leeds, England during more than 30 years from 1956 to 1988, noted that in the 1950s the average age of patients treated was 40 years; in 1960–1965, 45 years; in 1965–1970, 50 years; with a subsequent plateau around a mean of 60 years of age from 1975 onwards. More and more during the 1970s and since, renal failure was seen not as an isolated finding but in a setting of multiorgan failure [92] (a term probably first used in 1973) and sepsis, particularly the presence of a need for artificial ventilation. The need for two support machines immediately raised the mortality to three out of every four such desperately ill patients. Despite the many changes in management detailed above and in subsequent chapters, the mortality of 'acute renal failure' has, if anything, increased slightly during the past five decades (Fig. 16.2). But today it is a different condition, and occurs in different patients.

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Chapter 17

The 1970s and 1980s: new technical advances and some new problems

Dialysis dysequilibrium

The haemodialysis procedure itself turned out to have its own immediate complications as well as those of the now prolonged uraemia. At the beginning of the 1960s, much attention was paid to dialysis disequilibrium [1,2] in which the brain swelled as the concentration of solutes, mainly urea in the blood plasma fell below that within the brain, which exchanged its fluids only slowly. With smaller dialysers, slower dialysis and better understanding of solute transfer this ceased to be a problem by the 1970s.

Dialysis leukopaenia

In the late 1960s, the events following the exposure of whole blood to raw cellulose became better understood, with some frightening findings which, had they been known at the beginning, might have prevented haemodialysis using cellulose membranes ever being started. The most startling of these was the precipitate but reversible fall in the peripheral white cell count during the first half hour after beginning haemodialysis. This had been described by Nannie De Leeuw and Blaustein in 1949 [3] and was rediscovered by the Japanese [4], but these observations were overlooked and had to be rediscovered yet again in 1968 by Goffinet and colleagues [5] who described the sequestration of white cells in the patient as well as adhesion to the membrane. This was the beginning of studies into the '*biocompatibilty*' of the various materials used in the dialysis circuit. However, although this term appears to have been introduced around 1971 to describe reactions to solid implantable materials, the first paper I can identify in which it was used in connection with dialysis occurred as late as 1980 [6]. It was employed a couple of years earlier with reference to a charcoal perfusion circuit, however.

Only in the late 1970s and 1980s were the details of this bioincompatibility explored in detail. The 1936 and 1948 observations that cellulose, being a carbohydrate, could activate complement to produce chemotactic proteins [4] were rediscovered [7]; but with a fuller description of cytokines and leukocyte adhesion molecules made in the last decade has come a greater understanding of what is going on when blood meets membrane. Most of the newer membranes (see later in this chapter) have a lesser capacity to activate complement and induce leukocyte adhesion and release than cellulose acetate, but all are far from fully biocompatible, i.e triggering no inflammatory cascades and being non-thrombogenic.

Access for haemodialysis

An obvious weakness of long-term haemodialysis was the need to needle a vessel repeatedly. Single-needle access, with alternating withdrawl and re-injection of blood was introduced in 1972 by Kopp, Gutch and Kolff [8] which simplified the process, but the ideal was to have a permanent access implanted which required only connection. This seemingly simple goal has eluded all of the many attempts which have been made in the past 30 years to achieve it, which are summarized up to the end of the 1980s in references [9–13]. In day-to-day practice, there has been little change in long-term access technology since the 1960s, except for the introduction of woven polytetrafluoroethylene (PTFE) as a material for implanted subcutaneous arteriovenous grafts by George Thomas in Seattle [14].

One major practical advance in vascular access technology was made by Josef Erbén (b. 1926) in Czechoslovakia [14,15], namely the introduction in 1969 of *percutaneous subclavian lines* for intermediate-term access (Fig. 17.1), using the wire technique for insertion invented by Sven Ivar Seldinger in Sweden in 1953. This, whilst allowing freedom and rapid access to the circulation, has led to the long-term problems of subsequent subclavian venous stenosis with increasing pressures within the dialysis circuit as blood flow increases. Initially, Erbén used two separate single-lumen catheters, inserted either into the same subclavian, the opposite subclavian, or sometimes the femoral vein. During the 1970s this technique was explored extensively by Robert Uldall (1935–1995) and colleagues in Canada, who used long-term indwelling single-lumen catheters and is now in wide use for temporary access and in some (often older) patients as a long-term solution [16]. During the early 1980s, double-lumen subclavian catheters with little or no increase in overall diameter became available (first from the Vas-Cath Company of Canada) and were used widely until soft silicone rubber double-lumen catheters were introduced in 1988 (the PermCath). The use of the internal jugular vein in the same way came later, and recent developments of catheter access are well described by Twardowski [17].

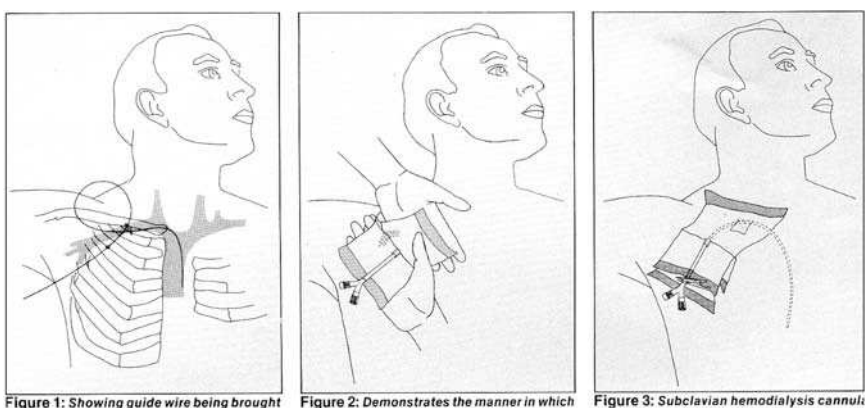


Fig. 17.1 A subclavian double-lumen catheter for haemodialysis. (From [16].)

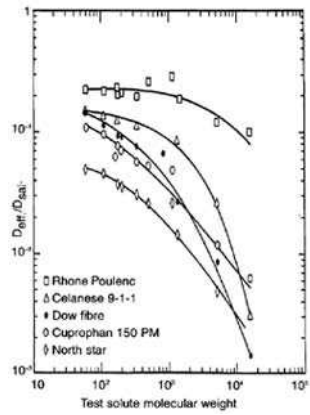
New membranes for haemodialysis

It was fortuitous that cellulose membranes from the packaging industry proved so useful as a substrate for clinical dialysis, and made it possible. In the form of cuprophan, despite the obvious disadvantages of complement activation and clotting, and the low cut-off in molecular size, this rather thick (11–20 μm) membrane was still the principal one in use, more than 50 years after its introduction. However, major efforts by industry to produce more permeable non-thrombogenic biocompatible membranes [18–20] have seen the proportion of patients using unmodified cellulose membranes fall to less than half during the 1990s.

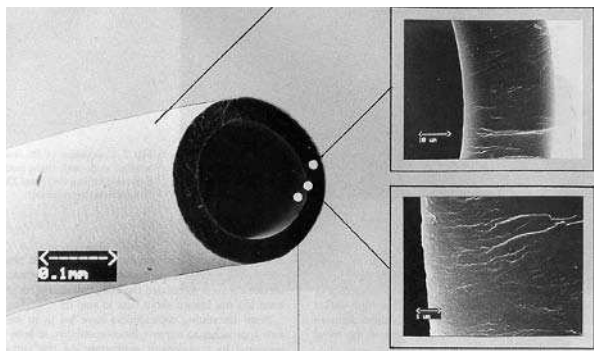
This search began in the early 1960s [21] when David Lyman of the Stanford Research Institute, CA with studies of polyester membranes derived from polyoxyetheylene glycol and polyethylene terphthalate membranes. The first synthetic to make a major impact, both in performance and clinically, was the French polyacrylonitrile-sodium methallyl sulphonate membrane, AN-69 [22], synthesized by A. Sausse of the Rhône–Poulenc Company in 1967 (Fig. 17.2). Because of its greater permeability, if it was used for dialysis rather than for convective removal of solute by ultrafiltration which had only just been described (see below), then it had to be used with a special closed circuit apparatus, different from all of the systems then in use. The capital costs of switching to the new membrane were therefore considerable, and ironically although it represented a major advance in dialysis technology, very few units adopted it.

Since then, many new membranes have been introduced, with the aim of higher permeability to large molecules and better biocompatibility. Cellulose has made a comeback, using new methods of regeneration other than the classic cuprammonium process of the 1890s via the new cellulose di- and triacetates, or xanthate. Completely new polymers such as polycarbonate, polyamide, polysulphone and others have appeared, many of which are in production and commercially available in dialysers, and which are detailed in the reviews of Vienken [18], Cheung and Leypoldt [20] and Klein [19].

These newer membranes differ in ultrafiltration coefficient, dialysance of small and/or large molecules, biocompatibility and suitability for re-use. The much more permeable membranes permitted major clearance by ultrafiltration as well as diffusion, and many allow larger molecules to clear more efficiently. This could be important in averting dialysis amyloidosis (see Chapter 18), although this remains controversial. Whether the choice of membrane makes a difference in terms of *outcome* to patients either with acute or chronic renal failure on dialysis is still topic of hot debate, although it now seems clear that a number of subjective and objective parameters are improved in those on chronic dialysis by the use of the newer membranes, including well-being and symptoms during dialysis, blood fats, cardiac function, infection rate and overall nutrition. Their use in exploiting their high permeability to larger molecules in order to remove solute by ultrafiltration has been explored extensively (see below), and again there seems little doubt that potentially and actually toxic large molecules, such as peptides and even small proteins, can be removed more efficiently. Again, however, there is only inconclusive evidence as to whether these apparent benefits lead to clinical improvement, prevent dialysis amyloidosis or prolong survival (see Chapter 19) [18].



(a)



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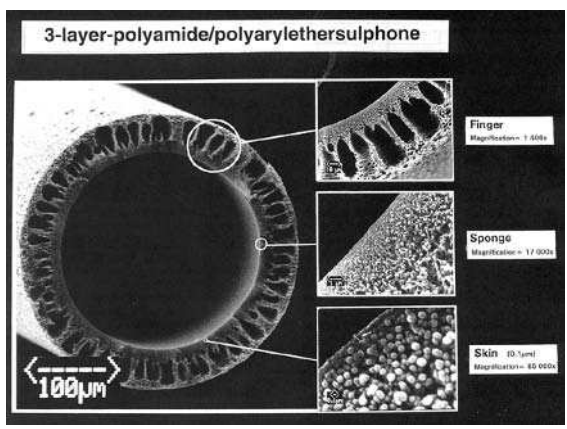


(c)

Fig. 17.2 Modern hollow fibres made from synthetic membranes. (a) The enhanced permeability of the revolutionary Rhône–Poulenc polyacrylonitrile (PAN) membrane AN-69 of 1968, especially for higher molecular weight solutes when compared with cellulose or cellulose acetate, is immediately evident. (b) A hollow fibre made of AN-69. (c) A modern triple-layer membrane fibre, the polyamide/polyarylethersulphone membrane of A.G. Gambro from 1996. The fibre wall is much thinner than the original AN-69 PAN fibre and, unlike the former's homogenous structure, has three structural components. (From [18] with permission.)

In fact, throughout the 1970s and much of the 1980s, the primary membrane remained cellulose acetate, at least in Europe. In 1980–1984, only 4% of patients were using the new membranes (mainly polyacrylonitrile), whilst another 4% used the 'new' type of cellulose membranes [9,23]. However, during the next decade there was a rapid increase in the use of synthetic membranes. In the United States, by 1990 16% of patients were using synthetic membranes, 14% of these high flux, and a further 18% modified cellulose; by 1997 this had increased to a total of 47% on synthetic membranes (27% low flux, 20% high flux) and 20% using modified cellulose [23]. Only 21% of American patients were dialysing in 1997 on unmodified cellulose membranes of the classic type, and this fell to only 16% by 2000, with 74% using synthetic membranes by then [24]. For Europe data are less completely available, but in 1999 approximately 55% of patients were using synthetic membranes and 45% traditional or modified cellulose, and a further 5% transferred in the subsequent year to 2000 [23].

New haemodialysis strategies: shorter or longer? More or less frequent?

In the continuing absence of any means of knowing how much dialysis should be done, or how to measure it apart from the length of the dialysis or the size of the dialyser, naturally many clinicans tried to examine different schedules of dialysis other than the (by now) standard thrice weekly sessions. It remains remarkable how little we know even today of what might be the optimum strategy for dialysis, in terms of patient rehabilitation, complications, convenience and—last but not least—cost.

The first question which arose is, when should dialysis be begun? In the overcrowded units of the 1960s this was not a question that could be asked: patients arrived in advanced, even terminal uraemia with many complications, ill and malnourished, and those that were treated at all were lucky. By the 1970s, when in many countries dialysis was now an organized activity, the folly of this approach became evident. The growing number of patients referred early and known to be in uraemia should start dialysis earlier, before complications had set in. But when, and on what criteria? In general, the strategy adopted was still to postpone dialysis as long as possible, so that when it finally started the plasma creatinine and urea concentrations would fall, indicating that the patients' own kidney function had fallen to a level even lower than that which conventional dialysis could provide. This point turned out to be a glomerular filtration rate (GFR) of about 3–5 ml/min or 2–4% of normal [25]. How the dialysis might translate into a sort of 'weekly GFR equivalent' was not clear, but in terms of small molecules was clearly providing a better service to the patient than his own remnant kidneys.

This view of a late starting point for dialysis was challenged first by Vittorio Bonomini (b. 1924) working in Bologna, Italy. In his unit during the late 1970s he experimented with taking patients on earlier, with a GFR (or creatinine clearance) of about 10 ml/min or even higher [26]. His patients were fitter and survived better in informal comparisons but—and it was a big but—there had to be the capacity to allow this liberal approach, and the start baseline was different thus making comparisons of survival difficult. I remember well the disbelief and envy that his work was

greeted with in the United Kingdom, where we had dying patients stacked up waiting for the next dialysis place to be released, happily by transplantation or sadly by death, in units crammed to capacity and working in permanent overdrive. Most units—even where facilities existed to permit it—did not adopt Bonomini's approach, however, until data had accumulated throughout the 1980s and early 1990s that patients treated late, either because they presented late or were kept waiting, did much worse in terms of both survival and complications [27]. We still do not know if this is true if those *presenting* late (i.e. previously unknown to the medical community) are excluded from analysis, and randomized trials of dialysis start time have proved difficult both to design and to execute.

However, the dramatic change in the 1970s in everyday practice was the startling reduction in the length of dialysis. The use of ultracompact capillary dialysers increased during the 1970s and especially the 1980s to become almost universal, and there was almost no limitation on the area of dialyser which could be constructed. As a result of demand, the Cordis Dow Company—one of the major capillary dialyser manufacturers and originators of the technology—built 1.5, 2.0 and then 2.5 m^2 dialysers; an area of dialysing surface not seen since the days of the rotating drum. Again, an Italian, Vincenzo Cambi (b. 1937) of Parma, took a lead role in promoting shorter dialysis schedules, using these larger surface area dialysers [28]. As we will see later in this chapter, when this approach began in 1974 there was still no means of quantitating dialysis, however inadequate the methodology, so this was an entirely empirical exercise. In retrospect, this approach immediately raised some relatively new questions. With longer dialysis, as hitherto performed, the patient's own residual function was not thought important. Everyone had observed a fall off in urine output in almost all patients started on regular haemodialysis, but no-one had measured how much the patient's own kidneys contributed. Ideas of solute removal by ultrafiltration were only just born (see below) so that the removal of urea by convection was not taken into account. Despite this ignorance of many important factors, during the 1970s the average length of dialysis in Europe halved from 8 to 4 hours.

Even then everyone was aware that the problem of what dialysis might be removing usefully was a major one. As new designs and models of dialysers flooded on to the market (over 400 by 1985 [23]) and schedules shortened, evaluation of their performance, especially their clearance of larger molecules such as vitamin B_{12} became even more important. Central programmes of dialyser evaluation were put in place in both the USA [29] and the United Kingdom [23]. However, in many countries, especially the United States, organizational and financial constraints in units whose government funding per dialysis was decreasing steadily throughout two decades [30] came to determine what dialysis patients received, and not what they might need. During the 1970s the length of dialysis sessions in the United States halved in parallel to Europe from 8 to 4 hours, and during the 1980s further reductions from 4 to 3 hours or even 2.5 hours took place. We are still living with the consequences of these changes. At that time in the 1970s, the outcomes of all the various different dialysis strategies appeared to be much the same and shorter thus seemed better. A word of caution was put forward as early as 1977 [31], and the first warning data came as early as 1982 when the European Dialysis and Transplant Society (EDTA) data for the

previous year showed that death rates were higher in patients using short dialysis schedules than those receiving longer dialysis [32]. By the end of the 1980s there were serious doubts about whether the reduction in the length of dialysis had gone too far.

Although not adopted widely by the dialysis community even today, the opposite philosophy has also been present throughout the past decades. Given that the kidney normally functions every hour and every day, surely the best treatment would be one which provides continuous treatment, or at least dialysis every day? The thrice weekly schedule popularized by Scribner included an awkward 3-day interval in each week, simply because the week contained 7 days! Surely at least alternate-day dialysis would be preferable to this quite arbitrary regime? Spurred by this idea, Bill Bluemle and his colleagues tried to calculate, in the 1960s, what the parameters for a dialyser operating continuously throughout 24 hours a day might be [33]. To provide the equivalent of a GFR of 15 ml/min (22 L/24 h) did not look impossible, and spurred many (including Kolff himself) to attempt to design, build and use 'wearable' artificial kidneys which would operate continuously. Despite these efforts, several practical problems, mainly to do with power supply and anticoagulation, prevented a truly wearable kidney emerging. Later, when haemofiltration was introduced (see below) the idea resurfaced as an 'artificial glomerulus' employing continuous filtration.

Daily dialysis was not only inconvenient for the patient, but access presented, and still presents, problems. Ironically, the abandoned external shunt might be best for this purpose, but failed too often and too soon. John de Palma and Mort Maxwell in LosAngeles [34] tried five times weekly dialysis on a coil dialyser and a shunt for access in patients doing badly on thrice weekly dialysis: all improved. This programme ran for 3 years before it was abandoned [35]. The ever innovative Vittorio Bonomini attempted daily dialysis for the first time in 1972 [36]. Two years later Zbylut Twardowski, then working in the Mining Industry Hospital in Bytom, near Cracow in Poland, compared two, three and four times weekly coil dialysis and fistula access [37] with the patients deliberately mismatched for residual renal function, those with greater residual function receiving less dialysis. Again, the frequently dialysed patients did better. Another programme of daily dialysis was started and ran for several years at the Maimonides Hospital in Brooklyn, New York [38]. This time reimbursement problems helped stop the investigational programme. Only in 1982 was a long running programme of frequent dialysis established by Umberto Buoncristiani of Perugia in Italy [39]. Seven years later, improvement in almost every parameter could be reported compared to thrice weekly schedules [40].

Finally, in the 1990s several groups began programmes of daily dialysis using innovative schedules and new machinery, and interest in this approach became widespread. Access could be by an indwelling subclavian catheter, which Bob Uldall had shown could last for a year or more [41]. These recent events are reviewed by Kjellstrand [35]. The costs, savings and benefits of this type of treatment are being investigated intensively today, and may provide the most physiological form of haemodialysis yet available. Obviously comparisons with continuous ambulatory peritoneal dialysis (CAPD) (see Chapter 19) immediately present themselves. At the time of writing the future role of daily dialysis remains uncertain, not the least

because the extra costs involved are not fully covered by government reimbursement in any country at the moment, including the United States.

Sequential ultrafiltration

All patients on dialysis require water removal as well as solute removal during dialysis, and the answer to water removal was utrafiltration by some means, using either hydrostatic pressure obtained by raising that in the blood compartment or lowering it in the dialysate compartment ('suck'), or by osmotic pressure. During haemodialysis this water removal was inevitably rather abrupt, two or even 3 days' worth of excess water and salt had to be removed—anything from 1 to 5 L, depending upon the self-discipline of the patient. This was done during the dialysis, and many patients felt awful during the procedure, some vomiting and others dropping their blood pressure, so that more fluid had to be infused. Then in 1976 Jonas Bergström (1929–2001) and his colleagues in Stockholm [42] stumbled by chance on to the idea that if ultrafiltration were performed at zero dialysate flow, so that no diffusion was occurring during the ultrafiltration, patients felt much better and this simple technique allowed more rapid removal of greater quantities of excess fluid. Stanley Shaldon found the same [42]. These observations were rapidly confirmed by many other clinicians, and became standard practice for patients with unstable circulation during dialysis.

Back to bicarbonate

Acetate had many advantages in practice as a buffer for dialysis systems involving continuously blended dialysate, which became almost universal. Thus from 1965 for 15 years this agent was standard. Early on it became clear that some patients tolerated it very poorly, feeling awful and with a persistent 'hangover' after dialysis, and later that some patients metabolized acetate to bicarbonate —which was what was actually needed—only very slowly. During the late 1970s and early 1980s systems which used bicarbonate as the buffer were introduced [43,44], and although more expensive gradually gained ground for at least these problem patients. By 1985, 15% of all patients in Europe were using this buffer, and during the 1990s it became standard.

Dialysate regeneration

Progress in designing dialysis systems was persistently inhibited by several constraints [20]: the most important was the lack of any clear target as to what was to be achieved in chemical or engineering terms by the process of dialysis, in the continued absence of clear ideas of what the uraemic syndrome was, or how it came about. Because targets were set using easily measured parameters such as urea clearance, new developments tended simply to be extensions of old, rather than radically new, approaches. Two rather more revolutionary ideas emerged in the late 1960s: one has remained in the background, whilst the other (ultrafiltration) has had a major influence on treatment of uraemia.

The idea which has failed, so far, to penetrate general dialysis practice to any extent is that of dialysate regeneration [45–49]. The large volumes of dialysate, especially in

single-pass open systems, were acceptable for static use, but if the idea of a wearable or even portable dialysis unit were to come about this problem needed to be solved. Absorption of dialysate with activated charcoal was tried [45,46] but had no effect in removing urea. In 1966, A. Johnson, an engineer of the Marquardt Corporation in Van Nuys, California suggested from his experience of purifying waste water from agricultural processing that this could be achieved. In addition, it would be possible selectively to elute uraemic toxins from the absorbate, and make them available for study. Drs Morton Maxwell (1924–2000) and Arthur Gordon were approached and expressed interest, and Dr L. Marantz was hired to explore what sorbents would be necessary [47]. A major, early and wise decision was not to try and absorb urea *per se*, but to lyse it to ammonia in the dialysate using urease, whereupon the ammonia could then be removed by cation exchange using zirconium phosphate [48]. This had the added advantage that it could be made in the form of hydrogen zirconium phosphate and help buffering of the dialysate. Calcium, magnesium and potassium are also absorbed by zirconium, so that calcium had to be re-added to the dialysate. Activated carbon formed the other major constituent of the regeneration cartridge. After work in dogs, studies were begun in humans in 1968 using the system [49], and the cartridge was released in the early 1970s for use in home dialysis. In the form of the REDY system (Fig. 17.3), this was in use mainly for remote or holiday dialysis, but has failed to make an entry into routine practice, although it is used in some situations such as the Australian outback for long-term dialysis. It has a number of disadvantages for long-term use, however [50].

Haemoperfusion using adsorbent materials

This topic strictly is outside the remit of this book, but has interacted with dialysis at several points during its development. The idea of using extracorporeal adsorption of uraemic toxins directly from the blood, rather than for dialysate regeneration, arose early as an idea for the treatment of uraemia, but has been even more handicapped than dialysis by the lack of information on exactly what needs to be removed to palliate uraemia and reverse its complications. One of the first applications in this area was the 'resin kidney' of E.E. Muirhead in Dallas, Texas in 1948 [51]; Muirhead employed a mixture of anion and cation exchange resins (Amberlite and Deacidite) already in laboratory use, which showed some capacity to remove urea as well as electrolytes. This 'kidney' was never used clinically, but in 1958 George Schreiner, with his major interest in poisoning, used an anion exchange column to remove pentobarbitone [52]. Exposure of whole blood to the resin, however, resulted in haemolysis, fever and electrolyte disturbances, and this approach was not pursued.

Later in 1964 at the first meeting of the newly formed EDTA, Hippocrates Yatzidis (b. 1923) from Athens reported on the use of uncoated activated charcoal, a powerful but non-specific adsorbent, in the treatment of uraemia as well as in the removal of ingested drugs [53]. Although it has remained a mainstay of perfusion studies, there were many problems with its use, principally thrombosis and platelet and white cell absorption on to the charcoal [54], and later charcoal embolization into the lung—so that it became clear very quickly that this agent could not safely be placed directly into

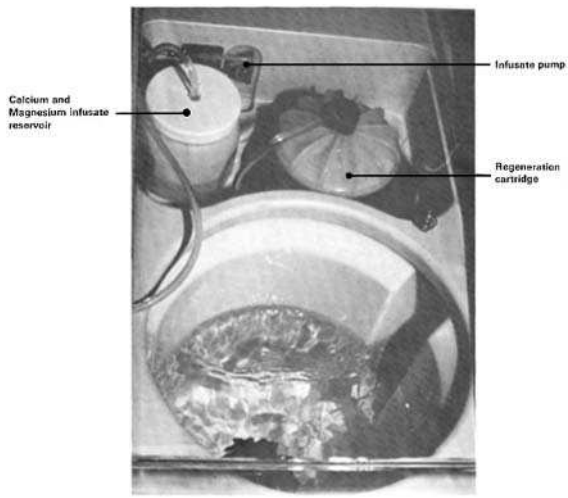
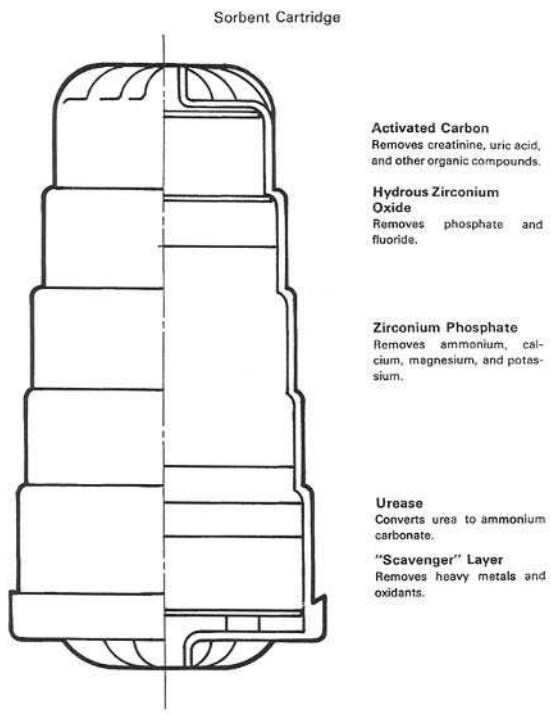


Figure 2. Top view.

(a)



(b)

Fig. 17.3 (a) The structure of a REDY cartridge for dialysate adsorption (From Klein [19], with permission). (b) The cartridge *in situ* (see text) (From Klein [19], with permission).

contact with the blood stream *in vivo* [55]. By the 1980s a number of systems had been evolved using charcoal coated with albumin or other materials, and/or ion exchange and other resins. These in general did not remove urea very well, or electrolytes and water, but adsorbed large amounts of ultraviolet-absorbing compounds of 'middle' molecular size (600–10 000 MW) such as phenols, guanidines and peptide hormones retained in uraemia.

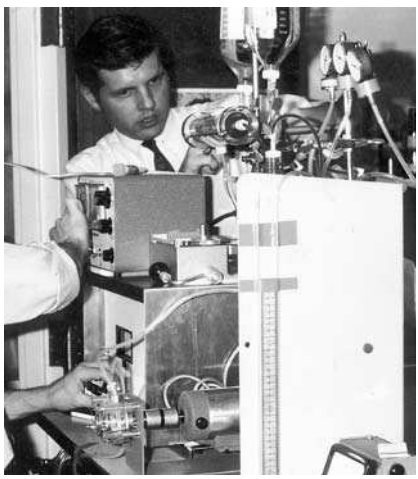
T.M.S. Chang worked for two decades from 1964 in McGill University of Montreal, Canada on the problem of encapsulating charcoal and other sorbents in microcapsules to use for the treatment of uraemia, pointing out that even 'large' 2 mm diameter capsules had a surface area of 2.5 m^2 in only 300 ml, and could perform as well as uncoated charcoal (see Winchester [56] and Chang [57] for a summary of this work). Because of the inability of the charcoal and resins to remove urea and possibly other non-polar metabolites, in general haemoperfusion for uraemia was done in parallel with haemodialysis to exploit the latter's excellent ability to remove small molecules (and above all water), and the former's ability to remove the (now, by the middle 1970s, fashionable) 'middle' molecules. Winchester [56] summarizes the short- and long-term results achieved up to 1986. Some of the most substantial studies were done in Vittorio Bonomini's unit in Bologna by Sergio Stefoni, but work was also done elsewhere in Italy, France, Scotland, Japan, Poland and other countries. Rather surprisingly, in view of the major interest in technical aspects of dialysis in the United States, little work was done there in haemoperfusion, although Lee Henderson did some studies and Jim Winchester took his interest from Glasgow, Scotland to Washington, DC when he emigrated there.

The idea of combined dialysis and perfusion did not achieve a place in the regular repertoire of treatment for chronic uraemia during the 1980s, however, not only because of the extra costs but also the relative complexity of the combined system, even if reduced dialysis times could be achieved. Poisoning has in fact proved to be the enduring field of use for haemoperfusion [55,56], although for a while there was major interest in treating hepatic failure in this way as well. It is interesting to note that following the use of dialysis for psoriasis and schizophrenia (see below), similar use was made of haemoperfusion techniques with the same initial enthusiasm and then disillusion [56].

Ultrafiltration and haemodiafiltration

In contrast, the impact of the other development, ultrafiltration in the forms of haemodiafiltration and continuous ultrafiltration has been enormous and lasting, particularly for the treatment of acute renal failure [58,59]. Until the late 1960s all removal of uraemic solutes was by *diffusion* of solute through solvent which remained static, based on Graham's work. Of course a small amount of solute was removed dissolved in the small amount of ultrafiltered solvent water which was taken out for volume control, or accidentally if the pressure within the blood circuit was particularly high. There had been laboratory work on bulk ultrafiltration using collodion membranes since the 1890s [60], which was reviewed by Arthur Grollman in 1926 [61], and the bulk removal of solvent and solute by this process of *convection* was routine in water purification. By the end of the 1920s, cellophane had mostly replaced collodion as the membrane used.

The first *in vivo* applications of ultrafiltration were reported by L. Brull in Liège, Belgium in 1928 [62] and Alexander Geiger in Jerusalem in 1931 [63], who both used collodion membranes. Later in 1947, M.R .Malinow and W. Korzon of the Michael Reese Hospital in Chicago built a device using cellulose acetate tubing 'to duplicate glomerular function', specifically in order to prolong life in uraemia, analysing the constituents of the ultrafiltrate and the selectivity of the membrane [64,65]. However, in dogs the removal rate for solute was very low and the apparatus was abandoned. It must be remembered that many of the pioneers of haemodialysis—Kolff and above all Alwall, as well as Skeggs and Brun—each studied ultrafiltration as a means of treat-



(a)

(b)

(c)

Fig. 17.4 (a) Lee Henderson and (b) Eduard Quellhorst who described independently the idea of convective removal of solute after initial studies on peritoneal dialysis during fluid removal, together with their respective machines. With the production of membranes of greater hydraulic permeability than cellulose acetate, this became a practical method of treatment (see text). (c) Henderson and Quellhorst with others who worked on chronic haemodiafiltration and acute continuous haemofiltration in the 1970s and early 1980s. From left to right, Juan Bosch, Karl Koch, Michael Lysaght, Lee Henderson, Eduard Quellhorst, Claudio Ronco and Conrad Baldamus. (courtesy Dr Claudio Ronco.)

ing patients with fluid overload, including for non-uraemic oedematous states such as the nephrotic syndrome and congestive cardiac failure [65], as Haas had suggested should be possible 20 years before (see Chapter 5). This remained throughout the 1950s and 1960s a therapeutic option used in patients with resistant oedema. The number of such patients declined during the 1960s when the highly efficient loop-acting diuretics were introduced, so this idea was temporarily neglected.

The idea of the convective removal of solute and solvent together was, however, not applied for the actual removal of solute as well as excess solvent water in uraemics, and it lay fallow until the work of Lee Henderson (b. 1930) and Bill Bluemle at the University of Pennsylvania in the United States [66,67] and Eduard Quellhorst (b. 1935) of Göttingen in Germany [68], during the mid 1960s (Fig. 17.4). Meyer Markovits and William Dorson, chemical engineers from Arizona, also did work on the subject at this time [67] although they did not take this further. It is interesting, as we have noted already in Chapter 15, that both Henderson [66] and Quellhorst [68] came upon the idea of convective solute removal independently through the study of peritoneal dialysis in 1966, noting that the removal of urea was significantly greater when fluid was being withdrawn in bulk using hypertonic glucose dialysate, as compared with dialysis alone without fluid removal.

Henderson at that time was working on new membranes for haemodialysis [67] and set about trying to see how much solute could be removed using the current cellulose acetate membranes prepared by the cuprammonium process. He says he 'can remember exploding a series of Travenol twin coils, trying to get sufficient ultrafiltration to confirm that convective transport worked across cellulosic membranes' [69]. However, the hydraulic permeability of cellulosic membranes clearly was too low for useful solute removal, as Malinow and Korzon had established, and it was the availablity of membranes of much higher permeability that Alan Michaels, founder of the Amicon Corporation had just synthesized which allowed the work to proceed [67]. Replacement fluid was added to the circuit immediately before the ultrafilter, whilst in Quellhorst's system the dilution was post-filtration [70,71]. Quellhorst's first membrane was from the Sartorius Corporation, but soon a completely new system was available—the Rhône–Poulenc RP-6 flat-bed dialyser containing a revolutionary new, relatively biocompatible and highly permeable polyacrylonitrile (PAN) membrane developed by A. Sausse [22,71,72]. The emergent hollow-fibre technology outlined above rapidly allowed compact disposable ultrafiltration systems to be constructed, which could combine dialysis and ultrafiltration as *haemodiafiltration* [67]. By the early 1970s both Henderson's and Quellhorst's systems began to be used in clinical situations [67,71,72], and the kinetics of the system were defined by Clark Colton, Henderson and their colleagues [67].

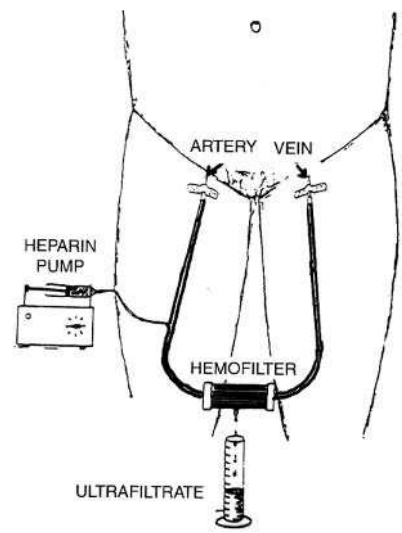
Henderson testifies that the major impetus for the development of haemofiltration was undoubtedly the development of the 'middle molecule' hypothesis by Babb, Scribner and colleagues in the mid 1970s. Scribner had noted as early as 1965 [73] that patients on peritoneal dialysis were notably fit, particularly with regard to reversal or prevention of neuropathy, when compared with their very high plasma creatinine and urea concentrations, or with patients on haemodialysis. The peritoneum was already known to allow the passage of molecules of a size considerably

larger than these small molecules. Could it be that more important to uraemic toxicity were these unidentified larger molecules? If so, then a method of removing them through a much more permeable ultrafiltration membrane would have great advantages, and this idea drove much of Henderson's early efforts. The 'middle molecule' hypothesis is discussed later in this chapter. Fortuitively, Bergström's observations in 1976 [42] on sequential ultrafiltration discussed above served also to direct further emphasis to the convective role of dialysis

Clinical use of haemofiltration techniques

It was in the field of *acute renal failure* that the technique was to have its major application, however. In May 1977, Peter Kramer (1938–1984) (Fig. 17.5a), also in Göttingen in the department of F. Scheler, began to use haemofiltration, first for the removal of excess salt and water [74] and then for the treatment of acute uraemia [75]. He realized from a fortunate accident [58,76] when a venous catheter was placed in the femoral artery by mistake rather than the vein, that a haemofiltration unit could be made very simple if it were placed in an arteriovenous circuit without pumps, and if used continuously could have great capacity used throughout the 24 hours. Thus *continuous arteriovenous haemofiltration* (CAVH) was born. This technique, and the many practical modifications it spawned [77], were to change the treatment of acute reversible renal failure completely [58,59,76,77].

(a)



(b)

Fig. 17.5 (a) Peter Kramer (1938–1984). (b) The simple arteriovenous circuit he introduced in 1977 for continuous arteriovenous haemofiltration (CAVH) had enormous influence on the treatment of acute renal failure (see text). Kramer died tragically soon, and did not live to see the full effects of his work.

Although there are few hard data to substantiate this statement, I recollect that in the year 1980 almost all patients in intensive care units with acute renal failure received haemodialysis using a dialyser containing a bioincompatible cellulose membrane thrice weekly, or on alternate days, under the supervision of a nephrologist, with the procedure carried out by a nephrology nurse based in a renal unit. A few patients were given peritoneal dialysis, but this was generally reserved for milder forms of single-organ acute renal failure managed outside the intensive care unit (generally in the renal ward or dialysis unit itself), rather than the increasingly complex patients, usually with multiple organ failure, now seen in intensive care units.

In complete contrast 10 years later in the early 1990s, 64% of European and 95% of Australian patients with acute renal failure in intensive care units were receiving haemofiltration in one form or another [78], using high permeability relatively biocompatible synthetic membranes, under the supervision of a specialist in intensive care medicine and supervised by critical care nurses based within the intensive care unit. Intensive care units in hospitals which lacked a renal unit, instead of referring the patient to a hospital with a renal unit for treatment, now performed one form or another of haemofiltration in their own unit [77], with or without any clinical nephrological input. These changes were evident earlier and more profoundly in Europe than in the United States where, according to Silvester and colleagues [78], the continuing involvement of both referring physicians and nephrologists remained greater in the care of their patients transferred to the intensive care unit.

How did this dramatic change come about? Curiously, it occurred without any unequivocal evidence that these continuous filtration-based techniques were any *better* than intermittent haemodialysis, even though there were many theoretical and actually observable reasons why this could be expected: stable volume control and gentler control of cardiovascular events, unlimited room for intravenous nutrition, steady lower concentrations of uraemic toxins of all molecular weights, and absence of a highly inflammatory cellulose membrane from the circuit were the principal reasons invoked [79]. Most clinicians had the impression that very ill patients 'tolerated' continuous ultrafiltration better than intermittent haemodialysis, especially from the point of view of troublesome hypotension. Faced with these facts, retrospective data comparing the two, flawed in all instances, were eagerly recruited to justify the change *post hoc*. However, no randomized controlled trials comparing classic intermittent dialysis (using incompatible membranes) with continuous forms of treatment (using more biocompatible membranes) were done for more than 10 years after their introduction—perhaps understandable in view of the theoretical, practical and even ethical difficulties of designing, organizing and carrying them out. When trials were finally designed and carried out in the late 1980s and 1990s, no clear differences in crude outcome as judged by patient survival emerged [78], although, as predicted, the return of renal function was a little earlier in the filtered patients. Finally, one is forced to conclude that this major paradigm shift in behaviour was powered as much by the cultural factors operating within hospitals and intensive care units as by the 'evidence' for—or more accurately the belief in—the clinical superiority of filtration.

These cultural factors involved first the responsibility for the patient. CAVH and related techniques permitted the intensive care specialist to take complete care of the patient if he or she wished to. 'Turf wars' occurred between general physicians, nephrologists and intensivists in many countries over the care of patients in acute renal failure requiring intensive care, most often because of a concomitant need for ventilation. The issue of whether continuous methods were superior was employed as a weapon in the battle, rather than explored as a field for scientific debate. Even by 1980 there were many more intensive care units than renal units in most countries—usually one in every major general district hospital—so the new technology allowed units in hospitals without a renal unit to treat their own intensive care patients in renal failure. Savings on the extra costs—for the critical care unit—of having a haemodialysis nurse come in to do the procedure offset the extra costs of the large volumes of expensive intravenous replacement fluids required. In contrast, CAVH in its simplest form at least, could just be part of the routine monitoring of the patient. This hit many nephrologists hard because, as discussed in Chapter 13, the use of dialysis for acute renal failure had been one of the crucial events promoting the formation of nephrology as a specialty. Some nephrologists felt that the slipping away of their responsibility for patients in acute renal failure and their associated electrolyte problems was a major blow to their identity and practice, and in several countries sometimes also to their incomes.

Despite the early work of Quellhorst and Scheler [72] and Henderson with his colleagues Cheryl Ford and Michael Lysaght [80], the impact of new filtration techniques on the treatment of *chronic irreversible uraemia* has been much smaller, largely because the high cost of the large volumes of replacement fluids needed for the treatment become a dominating factor in the longer term. By the mid 1980s in Europe, in contrast to the sharp increase in its use in intensive care units for acute renal failure as noted above, only about 4% of long-term patients were receiving this type of treatment. In countries with limited renal failure budgets such as the United Kingdom, it is virtually never used (only 1.4% of patients in 1991). In Europe as a whole, the proportion levelled out in the 1990s at 7.6% of patients (1.8% using haemofiltration alone and 5.8% haemodiafiltration) [81]. However, in a few countries such as Italy the proportion was much higher (1.9% and 17.6%, respectively), whilst in Germany, where the treatment was largely pioneered, the proportion remained low (3.0% and 3.0%, respectively, in 1991). Unfortunately, in the United States the United States Renal Data System (USRDS) data returns do not mention haemo(dia)filtration separately, nor do the Australian and Canadian reports, so one must assume that the uptake of this technique is trivial in these countries for long-term treatment today, presumably again for cost reasons. For example, dialysis remuneration is per procedure, at a fixed rate of around $125 in the United States, and extra costs of haemofiltration are not met.

Nevertheless, a number of possible advantages for long-term use of haemofiltration techniques have become evident [79,82]. The patients are fitter and feel better immediately after a treatment session. Blood pressure control is improved, and serum lipids revert towards normal. Survival of long-term patients, however, as in Quellhorst's first prospective comparison [83], has remained identical to that obtained by conventional haemodialysis.

The 'middle molecule' hypothesis

We discussed near the beginning of this book (see Chapter 2) some of the many theories which emerged from 1850 onwards to explain the toxicity of uraemia. However, from 150 years' work no single compound or groups of compounds has emerged to which we can attribute uniquely the clinical signs of uraemia [84]. Moreover, urea itself has emerged repeatedly as of little or no toxicity. The role of diet and of intestinal bacterial flora in addition to cellular metabolism itself in determining the appearance and concentrations of solutes in uraemic plasma has become evident. Further, the fact that residual renal function may persist for years in some patients on dialysis, whilst others become rapidly anuric, complicated understanding even more. This uncertainty as to the role of 'small' molecules such as urea and creatinine led to the idea that other, perhaps larger, molecules might be more important, which as we have seen was reinforced by the success of peritoneal dialysis in reversing uraemic neuropathy when haemodialysis (judged by the standards of the day as adequate) did not.

This uncertainty leads also to the conclusion that we have a treatment, dialysis, which clearly 'works' in palliating uraemia, without us having any clear idea of why this should be so; and in consequence the path to optimizing treatment is blocked. Intensive efforts were undertaken, principally during the 1970s and 1980s, to identify and study the hundreds of ultraviolet light-absorbing compounds of all molecular weights not present in normal plasma, which eluted from various fractionation columns when uraemic plasma was applied. Then these compounds were in turn tested in a variety of systems *in vitro* to see whether they were toxic [84,85]. In fact probably both small and middle molecules play a role, and the debate in the 1970s was rendered a little sterile by the strict adherence of protagonists in the debate to the idea that either one or the other must be important, to the exclusion of the other.

In fact, we know now also that some of these comparisons of small and middle-sized molecules were vitiated by misleading separation methods [85]. For example methylguanidine—a 'small' compound accumulating in uraemia—has undoubted toxic effects in *in vitro* systems, but in some systems elutes as a 'middle' molecule due to binding. Some truly 'middle' molecular weight fractions, such as the 7c chromatographic peak separated by Bergström and his colleagues [86] that has been partly characterized, are toxic also. The results have been, in sum, both inconclusive and confusing, and have not informed ideas of what 'adequate' or optimum dialysis might be. Gradually, as this intense investigation of uraemic plasma and dialysates failed to reveal any principal suspect toxic compounds, interest waned and is now at a low ebb.

The quantitation of dialysis: the dialysis index, URR and urea Kt/V

As far as conventional haemodialysis was concerned, although the kinetics of haemodialysis had been described by Wolff, Renkin, Bluemle and others [87–89] very early on, the 1960s ended without any clear methodology being available to quantitate the amount of haemodialysis delivered. Scribner's first patients were dialysed in

ignorance of what should be done for a 24-hour session once weekly. When several patients' neuropathy (which was common in patients starting dialysis then, as they were deep in chronic uraemia) failed to improve or worsened, this was changed to a twice weekly session of 11–14 hours, and then a thrice weekly schedule of 8 hours, all using the same 1 m^2 cuprophane Kiil-type dialysers. The duration of dialysis was regardless of age, sex or body mass or composition, and had been derived entirely empirically. Further, home dialysis overnight usually used long dialysis periods so that 8- or even 10-hour sessions were usual and remained so in units and countries with a high proportion of patients in home dialysis. The dialysers used were generally not powerful by later standards. During the 1970s, however, as more powerful dialysers became available the average duration of dialysis halved for operational, not physiological, reasons; the pressing need for some more accurate description of the quantity of dialysis was clearly evident.

Attempts to satisfy this need began with the 'square-meter/hour' of Babb and Scribner [90]. It had been obvious from almost the beginning that the size (power) of the dialyser on the one hand and the length of dialysis on the other were important variables in determining the efficiency of dialysis, but what was their relative importance? Was the removal of solute—in this case urea—the same when the duration of dialysis or the power of the dialyser was varied? Scribner suspected not, and that what was required was longer dialysis, perhaps to allow the unknown larger molecules to diffuse out of the patient. This could not happen adequately in shorter dialysis, however powerful or large the dialyser—yet the drive in the 1970s was the opposite, to reduce dialysis duration by using larger dialysers.

Debate has raged ever since—and continues today—over how best to quantitate dialysis, how much should be prescribed, how to ensure the prescription is actually carried out, and how this can be achieved using increased flow rates of blood and dialysate, larger dialysers and longer duration of dialysis. The deficiencies of urea as a surrogate marker for the unknown uraemic toxins has been mentioned above, despite some evidence that *in vivo* urea may be mildly toxic in interfering with some cell systems *in vitro*. Urea removal has been known since the pioneer days of dialysis to be strongly dependent upon blood flow rate, whilst less dependent on the duration of dialysis than larger molecules; in contrast the removal of solutes with a molecular weight of (say) 3–10 times that of urea (180–600 Da), which may be more signficant in generating uraemic toxicity, is relatively independent of blood flow above rates of 100 ml/min, but steadily increases with greater duration of dialysis [91]. Thus the putative universal measures of dialysis based on urea, introduced subsequently, have fatal flaws built into them even if empirically they correlate with some outcomes. Nevertheless, the failure of the advocates of the toxicity and importance of larger molecules to identify any compounds with specific effects (except β_2 microglobulin, discussed in Chapter 18) left the dialysis community with little alternative.

Babb went on from the square metre/hour hypothesis to develop a 'dialysis index' in 1975 [92] which took into account body surface area, residual renal function (the first time this had been highlighted as important), the clearance of vitamin B_{12} (MW 1355) not urea, the membrane used, and finally ultrafiltration to allow for convective transport. Although this had much to commend it theoretically, and an easy nomogram

was published to facilitate its use [93], it did not achieve any popularity. This was unfortunate because many shorter dialysis schedules tried out at that time and subsequently popular took no account of residual renal function or of convective removal of solute. These shorter schedules were immensely—and it proved dangerously—attractive to hard-pressed units who wished to get the maximum turnover from their limited facilities (and some would add, maximum profit), and to patients who (reasonably enough) also wished to spend as little time attached to a machine as possible and often voted with their feet rather than their heads.

This danger was reinforced by the widespread adoption of a urea-based index of dialysis efficiency, the *Kt/V* for urea, which was first described in 1985 by John Sargent and Frank Gotch [94]. The suggestion that this derivative of the general equation describing the urea concentration at any time point during dialysis might be important arose from a study of the data arising from the National Co-operative Dialysis Study in the United States. Outcomes in this study were correlated with various parameters, including the simple length of dialysis, and in this study *Kt/V* was found to predict mortality better than any other individual or combined set of data. Its calculation required a measure of the reduction in plasma urea concentration during dialysis, the duration of dialysis and an estimate of a volume of distribution of the urea, effectively the total body water. Of these, only the duration of dialysis is easy to measure with any precision, and the other two parameters are fraught with difficulties in practice: thus how to measure the *Kt/V* has become a highly contentious topic [95]. Even more contentious is whether it is the right measure to be making in the first place, but discussion of this recent controversy lies outside our scope here, and it remains unresolved. Our interest in it here is that it helped to divert attention and resources away from further work to identify the proposed 'middle' molecules, which appeared to be responsible for at least some uraemic toxicity [85].

Ed Lowrie and Lew [96] proposed the simpler idea that one component of the *Kt/V*, namely the reduction in the plasma urea concentration across dialysis, usually known as the urea reduction ratio or URR [95] could be used similarly. Some form of the *Kt/V* or the URR are now almost universally used as indicators of the amount of dialysis prescribed and delivered, and have become enshrined in recommended national and international standards. It remains to be seen whether this confidence is justified.

Dialysis for conditions other than uraemia

Although the subject of this book is the treatment of renal failure by dialysis, it is worth noting in passing the other indications which have arisen for dialysis.

Its use for the removal of poorly protein-bound water-soluble *drugs* when present in toxic quantities, or *poisons*, has been mentioned already. The first application for this was the removal of salicylate in a suicidal poisoned patient by Eric Bywaters and Mark Joekes in 1947 [97], and the removal of barbiturates by Alwall and his colleagues in 1953 [98]. Throughout the 1960s and up to 1977, George Schreiner, Jack Maher and their colleagues published in the *Transactions of the ASAIO* regular reviews of the dialysis of poisons using both haemodialysis and peritoneal dialysis [99]. One of the

more bizarre clinical trials in this area was the brief vogue for peanut or other oils as the dialysis fluid ('lipid dialysis'), to enhance the removal of fat-soluble sedatives such as glutethimide during the early 1960s [100]. The mess this made of the dialysis machine and surroundings were a major deterrent to the use of this technique! During the 1980s and since, adsorption techniques have come to be used as the principal extracorporeal method of drug and toxin removal from the body [56,101].

It is not surprising that dialysis was proposed for the treatment of diseases of unknown pathogenesis, since it was successful in the palliation of uraemia through the removal of what remain unidentified toxic or pathogenic substances. Thus, it was reasoned it might perhaps work in other diseases caused by other unknown dialysable substances. The fact that such putative dialysable agents would almost certainly be excreted by the normal kidney to some extent was apparently forgotten by many observers! Of course some effect of exposure to the bioincompatible dialysis membrane might mediate an effect, or even adsorption of the unknown toxins on to it.

Beginning with an anecdote of a patient from Joe McEvoy and his colleagues in Belfast, Northern Ireland in 1976, whose *psoriasis* went into and remained in remission [102], a number of other reports appeared [103] suggesting that coincident psoriasis improved in patients in renal failure undergoing haemodialysis. There was a brief vogue for systematically treating severe psoriasis in this way in the absence of renal failure [104], usually with weekly dialysis. Peritoneal dialysis was said to be effective as well [103,104], as well as (later) charcoal haemoperfusion. Theories were developed as to how it might act, and Zbylut Twardowski (who had first noted improvement in his psoriatic uraemic patients in Poland in the early 1970s) suggested that the toxic substance(s) might be filtered at the glomerulus but then extensively reabsorbed in the kidney, and thus dialysis could be of benefit. However, later there were reports of psoriasis developing in uraemic patients already on dialysis [105], results were generally disappointing in a notoriously variable and capricious disease, and the practice was abandoned despite the single small controlled trial apparently showing a favourable effect of peritoneal dialysis [106]. After about 1985, there was no more work in the area [107].

The use of dialysis to treat *schizophrenia* was suggested in 1960, even before long-term dialysis was available [108]. This idea lay fallow, however, until 1971 when James R. Cade in Florida and Herbert Wagemaker in Lousiville, KY used it on a woman, originally at her request. They were impressed with the results over the next few years [109] and studied its use further [110], analysing the dialysate for possibly relevant compounds and identifying an endorphin derivative in the dialysate. Naturally, public interest was considerable, and for a brief period at the end of the 1970s it seemed as though dialysis units were about to be overwhelmed with requests for this treatment. However, these results could not be reproduced [111] and although the topic surfaced intermittently for several years [112], problems of diagnosis and of assessing results were formidable. The results, including a single controlled trial in 24 patients [113], were equivocal and interest waned.

In the 1970s Frank Parsons in Leeds, England used dialysis in patients with advanced *malignant disease* to reduce the serum magnesium concentration, reasoning

from observations that the malignant cells would be more sensitive to this and might be inhibited or destroyed [114]. So far as I can ascertain the clinical results were never published.

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The difficulties of deciding even what question to ask of controlled trials are evident. There has been a parallel unresolved debate on whether, using haemodialysis, the choice of membrane is important in either acute renal failure or long-term dialysis (see: Jacobs C. Membrane compatibility in the treatment of acute renal failure: what is the evidence in 1996? *Nephrol Dial Transplant* 1997; **12**: 38–42; Himmelfarb J, Tolkoff-Rubin N, Chandran P, Parker RA, Wingard RL. Hakim R. A multicenter comparison of dialysis membranes in the treatment of acute renal failure requiring dialysis. *J Am Soc Nephrol* 1997; **9**: 257–66).

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95. The concentration of any solute—such as urea—in plasma at time t after starting dialysis (Ct) can be described by the equation $Ct = Co.e^{-Kt/V}$, where the starting urea concentration is Co. This can be re-arranged to $Kt/V_{urea} = \ln (Co/Ct)$. In Kt/V, which is a dimensionless parameter, K is the urea clearance of the dialyser, t is the duration of the dialysis in minutes, and V is the volume of distribution of urea in the body. It can be seen that the crucial input into this equation is Co/Ct, and this itself is often used as a crude index of dialysis adequacy as the urea reduction ratio (URR) = $100\ (1 - Ct/Co)$ [89]. The simple equation for Kt/V assumes, however, that all urea is distributed in a single pool. In fact at least two clear pools of urea can be distinguished both functionally and anatomically—within and outside the cells of the body. Thus a more appropriate calculation of Kt/V requires a two-pool rather than a single-pool model. When and how the post-dialysis sample for the estimation of Ct should be taken is crucial, since the concentration of urea in this sample varies as urea diffuses into the plasma from the cells and re-equilibrates within the circulation during and after stopping dialysis ('rebound'). Other problems are evident also: variable residual renal function may be present, and should be included in the calculation of total Kt/V. This summation assumes, however, that dialyser and kidney clearances are equivalent and can be summed, which although probably true for urea, is known not to be true for other, possibly more important substances of greater molecular weight. The notional volume V is unknown and can only be estimated from formulae (based on body weight and height) which, however, are often inappropriate in fluid overloaded and perhaps wasted subjects—such as uraemics. Finally, ultrafiltration and the urea contained in the ultrafiltered volume should be taken into account. The complete calculation of Kt/V thus requires a computer program, and any one of a dozen available 'shorthand' methods gives significantly different results. Therefore Kt/V, even if it does correlate with some clinical outcomes, falls hopelessly

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Chapter 18

A detective story: the rise and fall of aluminium poisoning—and a penalty of halfway technology: the rise and rise of dialysis amyloidosis

Aluminium poisoning: dialysis dementia

Towards the end of the 1960s and the beginning of the 1970s, a number of units who had been treating patients with long-term haemodialysis for more than a few years noticed the appearance of a tragic and bizarre syndrome in some amongst them. Even today, 30 years on, it is harrowing to watch contemporary films of these patients attempting to walk, eat or talk, or lying mute in their beds, emaciated and dying. When the first description appeared in 1972 [1] from Allen Alfrey and his colleagues in Denver, Colorado, at the 1972 meeting of the American Society of Artifical Internal Organs (ASAIO) in Seattle, others such as George Dunea's group in Chicago [2] (who coined the term 'dialysis dementia'), David Kerr and Nigel Wardle in Newcastle-upon-Tyne [3], Margaret Platts in Sheffield, England [4], and Jim Lawrence in Australia [5] immediately recognized the similarity of his observations to their own patients. The disease was evident also in other units in the United States, the United Kingdom and in Ireland, as well as in Japan. The description of this dreadful disease given later in an anonymous editorial in the *British Medical Journal* in 1976 [6] cannot be bettered:

> [It] may occur at any time after 15 months of haemodialysis—sometimes as long as seven years—and may be insidious or rapid in onset. The first sign is usually a speech disorder, most commonly stuttering or slurring of speech followed later by dysarthria, dysphasia, and sometimes mutism. Myoclonic jerks are constant, and all patients progress to global dementia. Psychological changes may also be present characterised by agitation, delirium, paranoia, and hallucination. Some patients have focal neurological deficits, most commonly a facial weakness, and some have convulsions. Early in the disorder the symptoms may be intermittent, being worse at the end of dialysis and improving before the next. In all cases reported the symptoms and signs have been progressive over periods ranging from 3 to 15 months, ending in death from suicide, pneumonia, septicaemia, or uraemia.

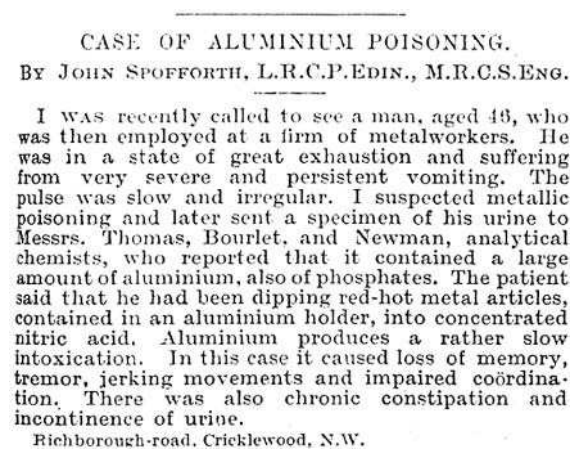
At first there was no idea as to the cause of the malady and Alfrey *et al.* concluded their paper with the statement that the cause 'remained undefined': accumulation of a toxic substance was considered, and metals such as tin [1], cadmium, zinc and lead [7] were considered, since they were known to accumulate in dialysis patients from contaminated dialysate [8]. Such intoxications, however, were only one possibility discussed alongside others: depletion of some vital factor by dialysis such as phosphate

[9] or rubidium [1,2], or a slow virus infection [5], or even mechanical problems with drainage of the cerebrospinal fluid [2]. Intoxication with some medicament was suspected, as many neurological syndromes appeared in uraemic patients from the accumulation of drugs or their metabolites.[10]. Platts and her colleagues observed shrewdly in 1973 [4] from observations in three affected men that:

> we strongly suspect there is some toxic substance in untreated water which, when used for long periods, is responsible for the neurological syndrome described, and probably for the increased frequency of bone disease. The substance is removed by a cationic resin exchange water softener.

Alfrey also had noted this possibility in his initial description [1], 'the sudden appearance of this syndrome in our chronic dialysis population suggested that a toxin, possibly coming from untreated tap water used for dialysis, might be responsible for this syndrome', but his and others' attention was diverted completely away from the water used for dialysis for more than a further 3 years, by the growing idea that the syndrome probably arose from aluminium intoxication—but that the route was aluminium taken by mouth. This possibility was not easy to investigate at the beginning of the 1970s because the measurement of these very small amounts of aluminium had not been standardized, and only with the advent of flameless atomic absorption spectrometry in the following years did it become fairly reproducible and reliable [11]. Technical problems persisted for another 5 years or more, particularly in extraction procedures, and above all in the analysis of tissue samples such as brain which led to some apparently anomalous results and conclusions.

Aluminium as a possible toxic substance was considered early on for several reasons. First, it was known to be a toxic element and (albeit rather rarely) capable of producing a neurological syndrome including dystonia and demetia (Fig. 18.1) [12,13]. It was widely prescribed to dialysis patients as aluminium hydroxide given by



CASE OF ALUMINIUM POISONING.

By John Spofforth, L.R.C.P.Edin., M.R.C.S.Eng.

I was recently called to see a man, aged 48, who was then employed at a firm of metalworkers. He was in a state of great exhaustion and suffering from very severe and persistent vomiting. The pulse was slow and irregular. I suspected metallic poisoning and later sent a specimen of his urine to Messrs. Thomas, Bourlet, and Newman, analytical chemists, who reported that it contained a large amount of aluminium, also of phosphates. The patient said that he had been dipping red-hot metal articles, contained in an aluminium holder, into concentrated nitric acid. Aluminium produces a rather slow intoxication. In this case it caused loss of memory, tremor, jerking movements and impaired coördination. There was also chronic constipation and incontinence of urine.

Richborough-road, Cricklewood, N.W.

Fig. 18.1 The 1921 *Lancet* 'paper' [12] of Spofforth describing the toxicity of aluminium, including dementia as a symptom. Used with permission. See Permissions.

mouth to control phosphate absorption, and was known to accumulate in uraemic patients in a time-dependent fashion [14–16]. Finally, it had already been implicated as a possible agent in Alzheimer's disease [17]. When Alfrey and his colleagues [18], using new methods of measurement, observed in 1976 high levels of aluminium in the brains of patients dying with dementia, they suggested reasonably that oral absorption of aluminium salts was the culprit, following Berlyne's suggestion [14]. There was, however, a problem with this hypothesis [19]. It had become evident that only a few units in some parts of the world were experiencing this dreadful epidemic. Many other units with large dialysis populations had never seen a case, despite liberal use of aluminium salts for more than a decade (Fig. 18.2), and heard of the experiences of their colleagues in amazement and horror only at second hand. How could this strangely patchy distribution be explained if oral aluminium was the culprit?

The vital clue came from an intriguing but unfortunate accident in the Netherlands [20]. In their unit in Eindhoven, Drs Flendrig and Kruis had experienced major problems with dialysis dementia from 1972 onwards, 3 years after they started their unit. Like almost everyone, they used aluminium hydroxide to control plasma phosphate concentrations, but there was something else: the other unit in the same town, using

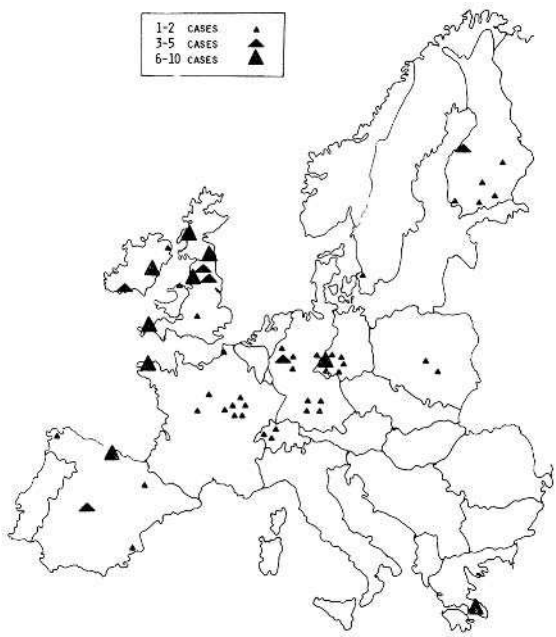


Fig. 18.2 The distribution of patients suffering from dialysis dementia in Europe. Many areas containing large populations of dialysis patients, such as northern Italy, London and the South East of England, and the Ruhr valley and its surroundings, saw no cases at all. In the United States, only about half a dozen units such as those in Denver, Chicago, Salt Lake City and Minneapolis had any patients, and in some of these areas not all units had affected patients. (From [33] with permission.)

the same water and also using aluminium hydroxide gel by mouth, had no such problems. They suspected something was wrong with their dialysis water, which was used untreated from the tap. Lead, copper and mercury concentrations were all as expected, but the aluminium concentration in the dialysate water was 20 times normal (1 instead of 0.06 ppm in tapwater). This water for dialysis had been heated in an electric boiler containing two aluminium anodes, together weighing 32.4 kg (70 pounds) which they now found had almost completely disappeared into the dialysis water over 2 years' use! They pointed out that the tapwater in both Ottawa [21] and Newcastle [22] contained considerable amounts of aluminium, because aluminum salts were used at the water works to clarify the water by flocculation, and they suggested further that the water used to prepare dialysate, as Platts had suggested 3 years previously, and not the oral alumium hydroxide gel as advocated by Alfrey, was the culprit.

Their hypothesis turned out to be substantially correct, although oral aluminum salts certainly do make a contribution to less dramatic aspects of the disease. The following year, Alfrey and colleagues demonstrated the transfer of aluminium into patients during dialysis [23]. In Chicago, Dunea and colleagues learned that from 1972 more aluminium had been added to their water supply, which they used untreated for dialysis, unlike most of their neighbour units who used deionizers to prepare it.

Platts [4], and Flendrig and Kruis [20], noted also that their patients had suffered a severe bone disease with spontaneous fractures, and at the meeting of the European Dialysis and Transplant Association (EDTA) later that year, when Flendrig and Kruis presented their data [20], in the same session Mike Ward, David Kerr and their colleagues from Newcastle presented the first detailed account of what came to be known (in Britain at least) as 'Newcastle bone disease' [22]. This consisted of spontanous fractures together with a pattern like osteomalacia on bone biopsy, with a myopathy affecting the proximal muscles of around the hip and shoulder but (unlike osteomalacia) normal concentrations of the bone enzyme alkaline phosphatase in the plasma, and resistance to treatment with vitamin D. Gerry Posen in Ottawa had already recorded in 1972 that patients using raw water—but not those using deionized water—could develop fracturing bone disease [21]. In addition, an unexpectedly severe and progressive anaemia was noted by workers in Glasgow, Scotland in patients with dementia [24]. This was related later to competition between aluminium and the iron essential for normal blood formation, such as in the competitive binding of aluminium to transferrin, the carrier protein for iron in the blood. Just as the deposition of increased amounts of aluminium was widespread throughout the body and not just in the brain and bone [18,20], so the manifestations of its presence were multiple.

The idea of aluminium as the toxic substance was accepted rather rapidly as other groups confirmed the aluminium accumulation in brain and other tissues [25]. In contrast, the idea that the water for dialysis was the principal culprit was not accepted immediately by all, with many observers still adhering to the idea that the main source was oral aluminium, especially in the United States. There, some careful and influential workers did not accept the role of aluminium even as late as 1979 [26] and

concluded, 'it is most likely that dialysis dementia has multifactorial causation and is probably not caused by the brain content of Al^{+3} alone' mainly on the basis that patients without dementia on dialysis also had raised brain aluminium concentrations, but to a lesser degree, as could other acutely ill patients with altered blood–brain barrier function.

Nevertheless, during these and the next few years, overwhelming evidence accumulated in the United Kingdom that the severity and pattern of aluminium intoxication mirrored closely that of the aluminium in the dialysis water supply both geographically and temporally [24,25,27,28]. The work of Margaret Platts in England [27] was particularly convincing, but in addition an epidemiological survey of the whole United Kingdom related the condition clearly to the water supply [28], whilst in the United States the pattern and timing of of aluminium in the water supply was obviously related also [29]. Reports of slow improvement after aluminium was removed from the water began to appear [30], and more serial observations and epidemiological studies put the matter beyond doubt [31–33]. It is interesting to see that this problem was solved, not by toxicity studies (which were in fact misleading), but by careful epidemiology.

It was now clear that the unfortunate patients had been caught in a trap created by events which had nothing to do with their renal failure, but lay in the water industry. In 'hard water' areas, the concentration of calcium was so high that water had to be treated in some way to remove this before it could be used for dialysis, otherwise the patients developed severe raised calcium concentrations in their blood. This meant that no untreated water could be used for dialysis in these areas, and even if some aluminium were present, it would be removed by deionization (although not by a conventional salt-exchange water softener). Only in areas of 'soft water' was untreated water used, and then only in some units. It so happened that in many of these areas the water was often discoloured with pigments from peat and other soils, which was removed before distribution for domestic use by treating the water, using variable amounts of alum to flocculate the material. In this process, soluble aluminium was introduced into the water. If the untreated water were used for dialysis—the only route to the outside for a patient with no renal function—then the aluminium accumulated progressively. The reason that proportionately so few American units saw affected patients was probably that in that country by 1970 most dialysis units already used deionizers for water purification regardless of its source, whereas this was not so in (for example) soft water areas of the British isles.

Apart from eliminating aluminium from the water used to prepare dialysate, what could be done to help these unfortunate patients? Even before aluminium was implicated, clearly this was a dialysis-related disease and some patients were transplanted to see if this would help. The early experiences (many of them never published or presented) were disappointing, probably because these unfortunates already had advanced and irreversible disease. However, soon reports of successful reversal following transplantation of less advanced cases appeared, although the aluminium was excreted only slowly [34]. No agent was then available to remove aluminium, but in 1980 Peter Ackrill, Tony Ralston and their colleagues in Manchester, England suggested the use of desiferrioxamine [35]. This was a compound which chelated

(bound) iron very strongly, but had also a strong (although lesser) affinity for aluminium. It had been used extensively by infusion to treat iron overloaded states, and they proposed it as treatment to mobilize and remove aluminium also, reporting a single successful case treated from November 1979 [35]. Much work published in the following 5 years or so showed that their suggestion was a good one [36] and that the treatment was effective.

As so often happens, in the dialysate–oral aluminium argument both sides were correct to some extent, and the syndrome was occasionally reported in patients with low aluminium in their dialysis water, as in Nashville, Tennessee [37], in those on peritoneal dialysis [38], and even in patients who had never received dialysis [39], especially children [40,41]; but always these patients were taking oral aluminium hydroxide. More subtle forms of the disease, such as the bone problems and the anaemia persisted as a clinical problem [42], usually assumed and sometimes proven to be the result of oral aluminium intake, and this rapidly became something for the dialysis community to avoid if at all possible. Other measures were suggested to deal with the need for phosphate removal, such as longer dialysis to keep phosphates low (but dialysis times were shortening everywhere and even prolonged dialysis was inadequate) and the use of calcium or magnesium carbonate. Only after another 15 years had passed did satisfactory aluminium-free phosphate binders become available, such as calcium acetate and sevelamer.

Today aluminium toxicity is not a problem in developed countries, although it surfaces here and there where control of water supplies for dialysis is not good, or aluminium absortion is facilitated. An unfortunate example of this was the interaction between citrate solution increasing aluminium absorption [43] leading to a full dementia syndrome. Aluminium remains a possible factor both in resistant anaemia and in resistant bone disease in patients on dialysis and in chronic renal failure. Water supplies are nowadays checked carefully for aluminium, the water industry is aware of the problem, and patients' serum aluminium levels are measured regularly. Nevertheless, other sources of aluminium accumulation for those in chronic renal failure have emerged, such as infant feeds [44], intravenous fluids and albumin solutions used for plasma exchange. The story of aluminium poisoning remains as a warning to physicians everywhere of how fragile and vulnerable the patient on dialysis is to changes in the minutest composition of the water they use for their life-saving treatments.

The rise and rise of dialysis amyloidosis

We turn now to a story which in contrast has, as yet, no happy ending: amyloid deposition in patients on long-term dialysis. This again was a completely new condition arising as a result of the use of dialysis, and unknown to medicine before. It illustrates the powerful ability of such 'halfway' technologies to create as well as solve problems. Beta-2 microglobulin amyloidosis remains the only clear example of a pathology arising directly in dialysed patients from the chronic retention of a toxic uraemic solute.

In 1975, independently, David Warren, a nephrologist working in Portsmouth, England [45] and E. Kinsey Smith in Hamilton, Ontario [46] noted that several of

their patients who had been on dialysis for a number of years had developed a carpal tunnel syndrome. That is, they had symptoms of pain, tingling and weakness from compression of their median nerves as they passed through the narrow tunnel at the wrist into the palm of either or both hands. Each of these papers apeared in general medical journals, so that many of those looking after dialysis patients did not notice them. If they did, their reaction was probably one of little surprise. After all, patients on dialysis were known to be fluid overloaded, and in some other fluid-expanded conditions such as pregnancy a reversible carpal tunnel syndrome could appear. Also, by 1975, almost all patients had an arteriovenous fistula in one limb at least, and the hand on that side was often a little swollen and engorged, with blood flowing distally into the hand as well as back into the anastomosed vein. This explanation seemed good enough to Warren [45], Smith [46] and several other clinicians [47] who described this syndrome within the next few years. Nevertheless this explanation did not stand up. Some of these reports noted no relationship to fistulae, some had had them in place for years, and in one report the symptoms occurred after the fistula had been closed. Moreover, lurking further down the list of causes of carpal tunnel syndrome was something else, much more rare and much more sinister: *amyloidosis*. Jain and his colleagues in 1979 [47] did look for this in the thickened flexor retinaculum of the wrist when it was cut to relieve the nerve, but 'special stains for amyloid were negative'.

'Amyloid' was given its inappropriate name by the great German pathologist Rudolf Virchow in 1854, because he believed this waxy substance to be made of a starch-like compound (latin: *amylum*) due to its staining properties, particularly because of its affinity for iodine. Inappropriate, because in fact it turned out to be a protein, or rather a group of proteins. All had several characteristics in common. First, insolubility and resistance to proteolytic enzymes, so that once deposited within tissues amyloid proteins persist almost indefinitely with very little removal. Second, a characteristic structure of β-pleated sheets of amino acids makes up the protein, which shows as fibrils of a regular diameter of 8–10 nm diameter on electron microscopy. This regular stucture also determines the properties by which amyloid was originally described—the ability to take very strongly certain stains such as iodine and thioflavine T, and the apple green dichroism (often inaccurately called birefringence) on staining with the dye Congo red, and viewing the sections under polarized light. When present in large quantities, the infiltrated tissue takes on a waxy or fatty appearance—hence the early German name for amyloid within the kidney of '*speckniere*' or bacon kidney.

By 1980 it was clear that many patients on long-term dialysis were developing this complication of a carpal tunnel syndrome, and the group of Guy Laurent and Bernard Charra at Tassin in France examined again microscopically the material they removed at surgical release of the median nerve in their dialysis patients with a carpal tunnel syndrome, and found to their surprise that it was not just fatty scar tissue, but had all the characteristic appearance and staining properties of an amyloid protein. This finding, reported only as a letter to begin with [48], was confirmed rapidly by others [49] and formally published [50]. But which amyloid was it? A number of proteins were known to be capable of precipitating to form amyloid fibrils, and the one

with a particular predilection for the carpal tunnel area was the free light chain of the antibody molecule γ-globulin, as in so-called 'primary' amyloidosis and that secondary to the malignant marrow dysplasia, myelomatosis. But in dialysis patients, the amyloid was negative on staining specifically for this, as it was for all other known amyloidogenic proteins, including the amyloid A protein found in amyloidosis secondary to chronic inflammation and infection. Some non-specific tests such as staining with potassium permanganate suggested amyloid A protein might be present, and misled several observers for a while.

The only solution to the problem was to extract the material and analyse its amino acid composition. This task was accomplished almost simultaneously in 1985 by two groups: by a Japanese–Boston collaboration led by Fumitake Gejyo and Alan Cohen [51] who studied material from the carpal tunnel of a patient who had been on haemodialysis for 13 years, and a group in New York and Nashville led by Peter Gorevic [52] who studied material from an amyloid-containing bone cyst. The result was a complete surprise: the amyloid fibrils in material removed from both patients appeared to be made of a small protein (MW 11 815), *β_2-microglobulin*, which had never been recorded as a cause of amyloid before. This was confirmed by specific immunofluorescence and amino acid sequencing on a further three patients [53] who all—importantly as it turned out—had been on dialysis for long periods of 8–14 years.

This small protein, β_2-microglobulin, had been described in the 1960s [54] as a constituent of unknown function in normal urine and plasma. In 1973, it was identified as a component of what were then known as HLA (human leukocyte antigens) [55] on the surface of some cells, mostly of the immune system. At that time these antigens were known only as tissue-typing antigens which had an influence on transplant outcome. It was shed slowly from the cells at a rate of about 100 mg/day, and broke down slowly. Furthermore, this β_2-microglobulin had been known for a decade to accumulate in patients in renal failure and in those on dialysis [56], and its concentration in plasma had even been suggested as a practical index of renal glomerular function. This arose because normally it is filtered through the glomerulus, because of its low molecular weight, and then is reabsorbed into the proximal renal tubule where it undergoes proteolysis. Although small enough to pass the permeable glomerulus with ease, it was far too large to pass through cellulose acetate dialysis membranes other than in minute amounts. As a result, the serum concentrations in patients on dialysis are enormous—in Gejyo's patients up to 40 times the normal concentration of less than 1.2 mg/L, and figures of 60 times normal were common.

Even worse, Gejyo's patients also showed amyloid in rectal biopsies, and several groups had already pointed out that other joints, in particular the shoulder and the neck [57,58], could be affected, with pain, stiffness and punched-out areas in the bone around the joint. In the Tassin unit, no less than 52 of 110 patients on dialysis for longer than 8 years had to have their wrists operated on, and three-quarters of these had stiff painful shoulders. Bardin and colleagues in Paris showed it was related to major problems in the neck: this was clearly a common and systemic and not a purely local disease [59]. Worst of all, β_2-microglobulin turned out to be a protein which very easily came out of solution and formed amyloid fibrils, more readily in fact than

any other previously known protein, since it could form amyloid without any prior breakdown with enzymes to degrade the molecule, as was the case with all other amyloid-provoking proteins [60]. Long-term dialysis, whilst saving their lives, had created a horrific new burden for patients in renal failure.

These new findings provoked an explosion of interest and alarm: more than 60 papers and abstracts were published on this topic in 1985 and 1986 alone, and within only a few years the problem had been mapped and defined [61–65]. From about 6–7 years on dialysis, patients began to develop deposits of β_2-microglobulin amyloid with a predilection for the joints and adjacent structures, particularly the wrist and hands, shoulder and neck; although only a quarter had clinical symptoms. By the time they had been on dialysis for 15 years, just about 100% of patients were affected, and by now almost all had symptoms [64]. These could be severe, with hands rendered almost useless by widespread amyloid infiltration, fractures through the weakened bone, and above all severe persistent pain. Some patients seemed not to get problems, but it was not clear what other factors might be operating. Iron and aluminium accumulation in the bone were suggested as localizing factors, but were dropped, as was the idea that crystals of the bone crystal hydroxyapatite in tissues might provoke precipitation. The predilection for joints and periarticular structures perhaps resided in the affinity for glycosaminoglycans in these structures, but the full reason for the pattern of localization still eludes us.

The single most important factor, apart from time on dialysis, in determining whether or not amyloidosis developed, seemed to be the age of the patients [66]: the young were relatively spared even on indefinite dialysis, and no child has ever been reported to develop this awful condition. However, those older than 45, and particularly the elderly, could develop the disease within only a few years. Why this should be so again remains obscure: one theory suggests that conjugation of the β_2-microglobulin with advanced glyscosylation products plays a role [66].

What could be done to help the unfortunate sufferers of this condition? [67] Apart from an operation on the wrist—which often had to be repeated again and sometimes yet again—averting the uraemia by transplanting the patients was the obvious action. This simply was not available for the majority, who already had been selected for and suffered long-term dialysis by unsuitability for transplantation on grounds of age, infirmity, associated disease or simple lack of available organs. However, those affected who were transplanted did report remarkable alleviation in symptoms, although, as expected, the amyloid deposits remained [68]. Much of this benefit, however, was probably the result of the corticosteroid treatment they received as anti-rejection therapy, and this treatment was tried in those still on dialysis, with benefit but the usual hazards and complications of prolonged corticosteroids. For a while it seemed as though peritoneal dialysis might be the answer, since to begin with no cases had been reported, and some were alleged to have improved on transfer from haemodialysis. However, at that time almost no patients had been on peritoneal dialysis long enough to develop amyloidosis, and when the threshold period was passed from 1986 onwards, patients on peritoneal dialysis proved just as liable to develop amyloidosis as those on haemodialysis [69]. This was less of a surprise when it became clear that their plasma concentration of β_2-microglobulin, although some-

what lower that in haemodialysis patients as a result of greater permeability of the peritoneum to small proteins, was still 20 or more times normal—rather than 30 or 40 times seen in haemodialysis patients.

Could ultrafiltration techniques or the new, more permeable dialysis membranes help? Again it seemed there was much greater bulk removal of β_2-microglobulin through the more permeable synthetic ultrafiltration membranes, but, as with peritoneal dialysis, better removal only resulted in a lowering towards a concentration of β_2-micoglobulin to about 20 times normal in the plasma, and patients treated using haemfiltration could develop the problem. Wholesale transfer of patients to newer highly permeable membranes and high-flux dialysis did not seem to be a useful strategy. Data did emerge suggesting that the cohort of patients in Belgium and France who had dialysed long term on the highly permeable AN-69 polyacrylonitrile membranes fared much better, but these data remained controversial [70]. An interesting and hopeful clue is that some of the lowering in β_2-microglobulin concentrations using synthetic membranes was the result of adsorption on to the membrane material, rather than their greater permeability, holding out the hope that an absorption system perhaps could be devised [71] and work continues on this approach using (for example) polymethacrylate. For a while, attention was side tracked on to the question of whether bioincompatible membranes, such as cellulose acetate, might actually lead to the release of more β_2-microglobulin from contact and breakdown of cells, but this turned out to be a red herring [72]. Today, the problem of dialysis amyloidosis remains unresolved. Some units have reported a fall in the numbers of patients affected [73], for reasons which are not clear, but this has not been a universal experience. Curiously there have been few reports since the initial papers from the United States, with the majority coming from Europe and Japan. Cynics unkindly remarked that the elderly patients in the United States did not, until recently, survive long enough to develop the condition!

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Chapter 19

Peritoneal dialysis transformed: CAPD

Peritoneal dialysis 1970–1978

Intermittent peritoneal dialysis continued to be a viable form of treatment for acute reversible renal failure during the 1970s, most often using the Maxwell technique and the Weston–Roberts catheter, but despite all the work of Henry Tenckhoff and other enthusiastic pioneers, peritoneal dialysis using implantable silicone rubber catheters and cycling machines played only a tiny part in the overall treatment of irreversible uraemia. A symposium in October 1976 in Seattle [1] summarized the position at that time in North America. A Veteran's Administration co-operative study was conducted from 1975 to compare peritoneal dialysis with home haemodialysis—probably the earliest controlled trial undertaken in the field of dialysis [2]. By 1978 in Seattle, 66 (15.8%) of their stock of 418 patients on long-term dialysis were using intermittent peritoneal dialysis [3] (some for as long as 4 years and an occasional patient for 8 years) and a total of 171 patients had been trained to use the technique, although it remained a minority interest. In Toronto under Dimitrios Oreopoulos' leadership [4] the technique was taken up, and 70 patients were dialysing in that unit by 1977, whilst in France Charles Mion [5], in Italy Umberto Buoncristiani [6] and in Australia Bob Atkins [7] were protagonists. In the United Kingdom, only the unit of John Goldsmith in Liverpool [8] had any number of patients on intermittent peritoneal dialysis during the 1970s. However, outside these enthusiastic units, in general the technique languished and was little used. The proportion of patients on dialysis receiving this form of treatment in Europe did not change, even though the absolute figures increased quite dramatically, so that even by 1978 only 839 patients out of 35 840 (2.3%) were using intermittent peritoneal dialysis, and probably no more than 500 or so in the United States. This situation, however, was about to change dramatically.

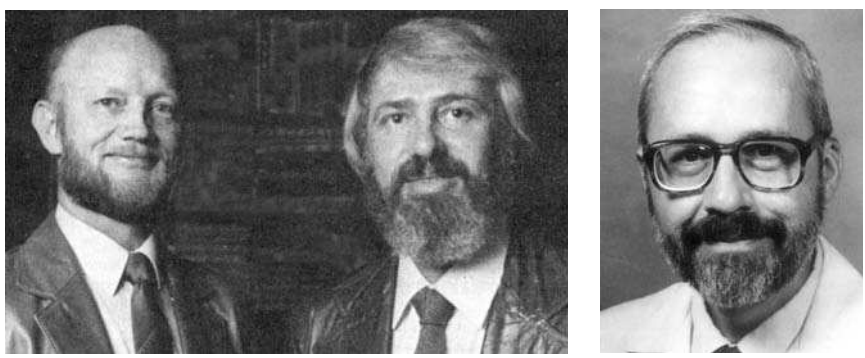
CAPD

Hitherto all patients had performed peritoneal dialysis on an intermittent basis, that is they dialysed for a period of 48 or even 72 hours once or twice a week continuously, normally using hourly exchanges. Fluid was contained in glass bottles which were bulky to store, especially at home, but the real problem was that despite the new silicone rubber catheters often there was rapid failure of the access to the peritoneum. Most patients were put on the treatment as a temporary measure, and few continued more than several months and fewer still more than a year or two. Peritonitis remained a problem, although Mion and his colleagues [5] were able to report

a peritonitis rate of as little as one episode per patient each 54 months, and Atkins [7] noted that half of their patients had never suffered peritonitis at all.

This intermittent schedule used hitherto had evolved empirically from regimes used to treat patients in acute renal failure, as had long-term haemodialysis. Now for the first time in the history of the whole subject of dialysis, a major advance occurred in a planned and predicted fashion based on a sound theoretical basis, rather than empirically. This development illustrates just what a small role science had played in the early years of dialysis up to the 1980s—almost all the analyses done hitherto were made *after* changes or innovations had been tried out in practice. The difference was that this time an engineer was involved.

The change originated in Austin, Texas in 1975 [9–13]. Jack Moncrief (b. 1936) (Fig. 19.1a, left) the nephrologist there practicing at the Austin Diagnostic clinic had a particular problem with a diabetic patient who did not do well on either of the two treatments currently available, and had major problems with access for haemodialysis, but wanted to remain in Austin. Moncrief discussed the problem with Robert Popovich (b. 1939) (Fig. 19.1a, right), a biomedical engineer in the University of Texas familiar with membrane kinetics from studies which led to the square meter/hour hypothesis for quantitation of haemodialysis [14]. Popovich suggested on purely theoretical grounds that, given an average size patient and average daily urea production, it should be possible to use continuous dialysis of five exchanges of 2 L each day with 2 L of ultrafiltration, using prolonged dwell times (4–5 hours) to produce *equilibrium* dialysis at a level of blood urea at about 160 mg/dL (27 mmol/L). As always, the most convenient molecule, urea, was used to perform the initial calculations. It is worth re-emphazing that Popovich's calculations involved a normal urea generation rate, a 70 kg individual using at least 10 L of solute exchange daily, plus 2 L of ultrafiltrate. All these important facts were in part forgotten during the next decade. Thus the peritoneum contained fluid throughout the whole 24 hours of the day—its strength was that diffusion could continue slowly and completely, but



(a) (b)

Fig. 19.1 (a) Jack Moncrief (b. 1936) (left) and Robert Popovich (b. 1939) (right), the inventors of CAPD. (b) Karl Nolph (b. 1937) who helped evaluate and popularize it.

this was also its weakness since unlike intermittent peritoneal dialysis there was no period of time with an 'empty' peritoneum during which the peritoneal cavity could build up any concentration of defensive cells or proteins against infection.

The idea was tested on the willing patient, and the actual results confirmed Popovich's calculations during the 5 months until the patient received a successful renal transplant. At first they used a change during the night to maintain the five exchanges and a 3–5-hour dwell time, but then changed this for convenience to four daily exchanges with the long dwell at night. Eagerly they submitted an abstract to the 1976 American Society of Artificial Internal Organs (ASAIO) meeting (Fig. 19.2)—and promptly had it refused for presentation, although it appeared in the abstract book [12].

By 1977 three patients had been submitted to this regime and a co-operative study was begun with sponsorship from the National Institutes of Health to evaluate the new treatment. Karl Nolph (b. 1937) of Missouri (Fig. 19.1b) joined the evaluation team, and the results on nine patients were reported in 1978 in a landmark paper [13]. A ponderous new name was chosen for the technique: *continuous*

THE DEFINITION OF A NOVEL PORTABLE/WEARABLE EQUILIBRIUM PERITONEAL DIALYSIS TECHNIQUE.

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An analysis will be presented which predicts that acceptable blood metabolite levels will result if 10 liters of dialysate per day are allowed to continuously equilibrate with body fluids. Accordingly, a portable/wearable dialysis procedure based upon equilibrium-intermittent peritoneal dialysis has been defined. Two liters of standard hypertonic dialysate fluid are infused peritoneally via a Tenckhoff catheter and allowed to equilibrate 5 hours while the patient conducts his normal activities. The dialysate is then drained and replaced with the procedure being repeated five times per day.

In a preliminary clinical study metabolite equilibration between blood and dialysate was achieved for BUN and creatinine but not for vitamin B-12. Steady state metabolite levels for BUN and creatinine were 40 and 9.5 mg% respectively. The patient was maintained 5 months with the new procedure with excellent clinical results followed by a successful transplant.

It is concluded that a new portable/wearable dialysis procedure has been defined. The technique does not require blood access and results in steady, low blood metabolite levels: middle molecule removal greatly exceeds that of conventional techniques.

Fig. 19.2 Moncrief and Popovich's abstract to the ASAIO meeting of 1986 first describing CAPD [12], which was turned down for presentation.

ambulatory peritoneal dialysis, fortunately abbreviated to CAPD, with which we are now stuck. By definition this was a self-administered technique which could be done at home, at work or anywhere the dialysis fluid could be made available; and this was a problem. CAPD worked, but a major difficulty was the fact that a clumsy, heavy, bulky glass bottle had to be disconnected and then a new one connected every cycle. Even worse, the peritonitis rate was horrendous (one episode every 10 *weeks*) [12], far worse than that usually achieved using the despised and neglected intermittent peritoneal dialysis. The problem was that in the United States, fluids for intravenous use could only be sold in stoppered glass bottles, even though fluids in polyvinyl chloride (PVC) bags were already licensed and available in Canada and Europe.

CAPD becomes the major treatment choice

Thus it was that in Toronto, Dimitrios Oreopoulos (b. 1939), who had trained in Belfast in Northern Ireland—where he first encountered peritoneal dialysis—and had then emigrated to Canada, ran one of the most active units in the field, employing the Lasker cycler. Oreopoulos immediately saw the potential of the new technique, and in September 1977 he started patients on CAPD using 2 L of fluid in 3 L PVC bags which could be run in, rolled up and carried about under the clothing until required for drainage, thus halving the number of disconnections [15]. Moreover the ends of the giving set were modified to a 'spike' which could be pushed through the cap of the bag. Immediately the peritonitis rate fell to one episode every 8 months—still an unacceptable level, however. In September 1978, plastic bags were licensed by the Federal Drugs Agency (FDA) in the United States. When a conference was held in 1981 on the subject [16] nearly 200 US units and many others all over the world, including a number from Britain, amongst them our own unit, had started putting patients on to CAPD from 1978–1979. Major attractions were that dialysis places within the dialysis unit were not required, and the training period of only a few weeks was mercifully short. Moreover, patients liked the relative freedom the technique allowed them, although the time occupied in performing the exchanges each and every day remained a burden. A number of patients who had transferred from haemodialysis seemed much fitter and better nourished on CAPD, and their haemoglobin concentrations rose and remained above those found in patients on haemodialysis [17]. This comparison, alluded to in Chapter 17, was and remains difficult [18].

The peritonitis rate still remained too high, but major advances to reduce this were the addition of a light titanium connector at the end of the catheter by Nolph in 1979 [19], and the introduction by Buoncristiani's group in Perugia, Italy, of a twin-bag system employing the 'flush before fill' technique in 1981 [20]. In a way scarcely seen in clinical dialysis until that time, this technique was evaluated promptly and carefully in a prospective randomized controlled trial [21], and proved to work as well as its originators had suggested. One episode of peritonitis every 2–3 years immediately became the target to aim for. Some years of scepticism and a further controlled trial, however, was needed before North America was convinced that the technique was worthwhile, but this also confirmed its worth in reducing the frequency of episodes of peritonitis beyond doubt [22].

Social and fiscal aspects of CAPD

The number of patients on long-term peritoneal dialysis catapulted rapidly upwards all over the world [16], but a strange pattern evolved. By the end of the 1980s and early 1990s in some countries the majority of patients were using already some form of CAPD (Figs 19.3 and 19.4), whilst in others—such as the United States—the proportion rose only to 15% or so, and stayed there (see Table 21.1). Children, diabetics and the elderly continued to form a disproportionately high component of the CAPD population, when compared with haemodialysis. Why was this?

The reasons were not medical, but political, organizational and fiscal [23]. Self-administered CAPD was undoubtedly cheaper than in-centre haemodialysis, and in a number of countries with central health provision, cost containment was a major goal. As discussed in Chapters 21 and 22, everywhere the soaring costs of dialysis were causing a growing concern in government circles; perhaps CAPD could provide an answer to the problem of limiting costs. In the United Kingdom there was an additional powerful stimulus to use the technique, providing an example of collateral, non-medical factors determining the use of a technique. Apart from its intrinsic attractions, these account in the main for its very rapid growth in that country. In Britian, those running dialysis units had to provide what they could within a pre-negotiated budget, which was not sensitive to the volume of patients treated or to the number of dialyses performed. Even more attractive, within the structure of the health service once a patient was at home it was possible to transfer the costs of the dialysis fluids from the hard-pressed renal unit budget, at first on to the pharmacy budget for intravenous fluids, and when this practice was blocked by the government, on to the budget of the family practice responsible for the patient, if they could be persuaded to prescribe the fluids for use at home. Thus in the United Kingdom the doubling of dialysis provision during the 1980s was almost entirely through the addition of patients doing CAPD, with almost no expansion in central or satellite haemodialysis units, purely driven by fiscal considerations and to the detriment of

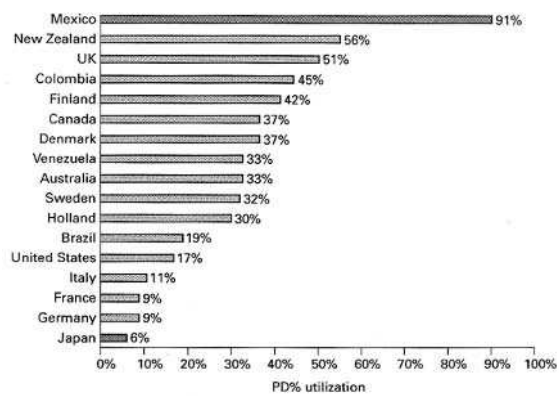

Fig. 19.3 The proportion of patients using CAPD in different countries in 1993. (Data courtesy Baxter Laboratories.)

(a)

(b)

Fig. 19.4 The fall in the proportion of home (HHD) as home CAPD was introduced in: (a) Europe and (b) the United States. (From Jacobs C. *J Nephrol* 1999; **12** (Suppl 20): s48, with permission.)

patient choice and balanced availability of treatments. Throughout the 1980s the number of main dialysis units remained at only a little above one per million total population—a figure 3–5 times less than that in most other European countries. The result was that in the United Kingdom many patients, especially the most elderly, were uniformly placed on CAPD at home. There, many quickly or eventually failed to manage the technique and had to return to in-centre haemodialysis, sometimes as emergencies, throwing an impossible load on to these already overstretched facilities. Thus a crisis in the early 1990s was inevitable, predictable, and occurred. In other countries such as Canada and Australia a widely scattered, sparse population over much of the country made the treatment particularly attractive, but in truth it must be admitted that finally it was the role of enthusiasts for the treatment such as Dimitrios Oreopoulos and later David Churchill in Canada, and Bob Atkins in Australia, that made the real difference.

Naturally, comparisons of all aspects of care—costs, outcomes, patient preferences, convenience, durability—were made everywhere between haemodialysis and CAPD. These were difficult to assess to begin with, because the patients were not comparable. In general patients having problems with haemodialysis, or excluded from it by lack of dialysis centre places or by age, and from transplantation by accessory diseases or age, tended to be started on CAPD. This resulted in high extra costs for hospital admissions and the other cost burdens of non-renal disease which the patients suffered from in addition. A particular group who tolerated the procedure well was the growing number of elderly patients on dialysis, whose less robust cardiovascular systems adapted well to the gentle continuous peritoneal dialysis as compared with the rugged intermittent haemodialysis and ultrafiltration. Naturally the survival of this group was limited by their greater age at entry to treatment. In addition, CAPD was used preferentially in many units for diabetics (see Chapter 20), who because of complications of their primary disease fared and survived less well. Because and through this 'de-selection', critics branded CAPD as 'a second class treatment for second class patients' [24] and some privately and cynically added 'carried out by second class doctors'. If, within nephrology, dialysis was still looked down on by those undertaking (for example) physiological or immunological studies, then peritoneal dialysis was regarded by many as the bottom rung, even of dialysis. This perception has been slow to disappear—if it has, even today.

However, after a decade of argument it became apparent that in *comparable patients*, the results were about the same using either treatment, both in terms of days spent in hospital and in crude survival [25], and that for many purposes (such as brief dialysis in preparation for a transplant) it had many advantages. In infants and children also, after the initial attempts in Canada [26] it became rapidly the standard form of dialysis [27] and many preferred it for their diabetic patients over haemodialysis (see Chapter 20). There was one major difference, however, between CAPD and haemodialysis: failure for technical reasons was far more common in CAPD than in haemodialysis [28], often from a gradual failure of the peritoneal membrane as a dialyser [29], visible histologically in biopsies as thickening [30]. Few patients continued to use it beyond 10 years [31], whereas patients could—and eventually did—survive more than three times as long using haemodialysis.

Peritonitis—a continuing problem

The pioneers of peritoneal dialysis in the 1930s, 1940s and 1950s had to cope with peritoneal infections in their acutely dialysed patients, initially without antibiotics. Then, and right until the beginning of CAPD in the late 1970s, most physicians regarded peritonitis in dialysed patients as no different from that in a surgical patient with an injury contaminating the peritoneum. This naïve attitude was rapidly shown to be incorrect, for several reasons [32]. The first was an obvious clinical one, that the organisms responsible for peritonitis in dialysed patients were quite different from those in surgical patients, being mainly staphylococci and streptococci, with only a minority of Gram-negative bowel organisms such as *Escherichia coli* or *Pseudomonas* spp. The second was that the dialysed peritoneum was predictably a very different environment from the normal peritoneum. In the dialysed peritoneal cavity, there is a

(relatively) huge volume of 2 L of (in CAPD at least) permanent indwelling fluid, and its immunology differs greatly from the normal peritoneum, which contains only a few hundreds of millilitres of fluid rich in defensive macrophages and proteins [33]; these are diluted down to negligible concentrations during CAPD and are maintained at low concentrations. Even worse, as first recognized by Cunningham in 1920 (see Chapter 6), the peritoneal dialysis fluid was seen to be toxic to the mesothelial lining of the peritoneum, so that its valuable protective functions were suppressed, and moreover the fluid inhibited the activity of the few macrophages present in the peritoneal contents [34]. But worst of all, while the normal peritoneum was sterile, it became clear during the 1980s that the indwelling dialysis catheter almost *inevitably* became contaminated by a resident population of adherent, usually slime-producing bacteria [35]. Signs of continuous low-grade inflammation within the peritoneum were present in the form of activated complement and inflammatory cytokines. Critics could refer to CAPD cynically as 'continuous ambulatory peritonitis'.

A widespread search for factors which might determine or undermine the defences of the peritoneum began and continues. New problems arose as it became clear that although the relatively mild episodes of infection from skin organisms contaminating the catheter tunnel, such as *Staphylococcus albus*, had indeed been drastically curtailed by the 'flush before fill' systems, those arising from the much more serious *Staph. aureus* and Gram-negative organisms such as *E. coli* and *Pseudomonas* spp. were not affected [36], and possibly became more common. One of the most important observations was that individuals who were carriers of *Staph. aureus* on their skin and in their noses were much more likely to have peritoneal infection than those without, so that a search for, and treatment of, this bacterial carriage was worthwhile [37].

How much CAPD? New styles of CAPD

As with haemodialysis, the question of what might be an 'adequate' amount of dialysis inevitably arose. During the 1980s a 'one size fits all' regime of four times 2 L exchanges daily was widely used and became standard. This was clearly less than that recommended originally as necessary from Popovich's calculations, which implied that dialysis needed to be individually prescribed. Given the greater permeability of the peritoneal membrane, small solutes such as urea and creatinine were even less valid for study than with haemodialysis. Nevertheless, these battle-worn and decidedly tired old war horses were pressed into service yet again to provide some mathematical expression of how much dialysis different patients of different sizes and with different renal function might require, either as a minimum or as an optimum.

The first attempt to describe adequacy was the 'peritoneal dialysis index' of Brendan Teehan and colleagues [38], which grew directly out of the style of Popovich's original calculations: how much dialysis would a person of a given size and nitrogen intake require to stabilize his or her blood urea at an arbitrary acceptable level? Later methods of estimating an equivalent to the Kt/V urea were developed [39], or a peritoneal creatinine clearance was calculated [40]. It was clear very early on that the 'standard' regime was indequate for all but small individuals who had retained residual renal function, which was additionally capable of excreting large molecules. In 1983 an

important observation was made: that using peritoneal dialysis, residual renal function persisted longer and at higher levels than after starting haemodialysis [41]; but despite the finding in this initial study that renal function actually remained stable during peritoneal dialysis, further data showed that in almost all patients, alas, there was a gradual fall-off in function [42]. The worst news was that in the majority of patients, this loss of native kidney function gradually took the total level of solute removal below that which could maintain the patient healthy using conventional dialysis.

A further measure was needed to give some indication of how permeable the peritoneum was, especially as it was recognized that this could gradually decline. Zbylut Twardowski (b. 1937) now having emigrated to Missouri, USA, introduced the idea of the peritoneal equilibration test (PET) in 1987 [43] which has now become standard. In this, glucose transport out of the peritoneum is studied over a 4-hour period, and the rapidity of disappearance is characterized into four categories from high to low peritoneal transport rates. In those with very rapid loss of glucose from the peritoneum into blood, the osmotic gradient quickly lessens and adequate ultrafiltration is not possible. At the opposite end, removal of solute can become progressively poorer in those with low transport characteristics.

Inevitably the idea of combining cycling machines with CAPD arose both for convenience and to increase the amount of dialysis that could be achieved, and perhaps the first exploitation of this was in Wadi Suki's unit in Texas in 1981 [44] where rapid machine cycling was used overnight, together with a long daytime dwell period. This was called CCPD, for continuous cycling peritoneal dialysis. Several variations on this theme using different schedules of dialysis have been suggested and used since. Later in the 1990s, machines became popular for automated peritoneal dialysis (APD). The impetus came largely from the patients themselves, for whom the four or even five daytime exchanges took several hours out of the day. However, this development represented a departure from the idea that the technique should above all be a simple, cheap, rugged process, requiring no machinery and only brief training. In fact, costs for home haemodialysis and standard CAPD were about equal everywhere, but the use of machines took the cost of CAPD well above that of home haemodialysis, although it still remained cheaper than in-centre haemodialysis.

Sclerosing encapsulating peritonitis

Just as long-term haemodialysis produced unexpected long-term disastrous complications, so did CAPD. As early as 1980 the first report appeared from Chicago [45] of terrible sclerosis within the peritoneum in patients who had undergone intermittent peritoneal dialysis for several years. This was followed within a few years [46,47] by reports of occasional but similar patients from all over the world receiving CAPD—the majority from Europe. In these patients dialysis failed, and at catheter removal the peritoneum was thickened and enveloped the small bowel, so that on looking into the abdomen at operation it was said to resemble the inside of an enamel bath. The patients were ill, feverish, suffered progressive malnourishment from intestinal failure and eventually died if they were not transferred on to haemodialysis—and often died even when they were. The condition could appear

even after peritoneal dialysis had ceased, and mortality varied overall from 50% to 90%. Clearly this unprecedented finding was a function of the dialysis, but which aspect was responsible? In 1985 the European Dialysis and Transplantation Association/European Renal Association (EDTA-ERA) undertook a survey of European dialysis centres to try and tease out the epidemiology of the problem. Only one factor of dozens of possibilities examined seemed to be associated with its appearance: the use of the antiseptic chlorhexidine to flush and sterilize the peritoneal catheter, so that it might contaminate the peritoneal cavity [48]. Nevertheless the condition has continued to occur in patients [49] who have never used chlorhexidine, and seems recently to have become more common again. Acetate buffer was suggested as a possible cause also, which resulted in its withdrawl from fluids for peritoneal dialysis during the 1980s, with lactate substituted instead.

New dialysis fluids

The acidity (low pH) and high osmolality of the usual fluids have been—and remain—a challenge to the ingenuity of the dialysis community [50], since they result in progressive damage to the peritoneal mesothelial lining by glycation of proteins and effects of the low pH, and inhibit the activity of the diluted peritoneal macrophages. The concentration of electrolytes was more or less standardized very early, the major points of contention being the exact concentration of sodium and what calcium concentration was optimal given the complex disorders of bone and its hormonal control present in uraemic patients. We have seen above how dextrose became the standard agent for inducing osmotic fluid loss right from its use in the 1920s, and with acute dialysis there was little stimulus to change—except in diabetics. Those diabetics with acute renal failure and hyperosmolar coma already had very high blood glucose concentrations, and posed a major challenge to the use of peritonal dialysis for their treatment. As a result, sorbitol was investigated and produced commercially (Peritofundin-S, Braun Pharmaceuticals) and used for a few years in the late 1960s. Later, Giorgio Bazzato in Venice investigated another compound, xylitol, for the same purpose but it was not used otherwise. Similarly glycerol was used, but diffused too rapidly to be of general use although still retaining some attractions in diabetic patients. During the subsequent decades other substances were tried as generally useful osmotic agents, particularly various amino acid solutions. However, these remain expensive and prone to induce acidosis, and are usually reserved only for nutritional reasons.

An alternative approach to all these low molecular weight substances is to use high molecular weight substances. Gelatin 5% had been used in the 1940s by Fine and his colleagues [51], and was revived briefy in the 1980s in the form of its isocyanate (Hemaccel®) which was used as a plasma substitute and was available commercially. Dextrans were first used in the 1960s and revived in the 1980s, but, as expected, accumulated in plasma and tissues, and were abandoned. The only new osmotic agent to have become established in clinical practice is polyglucose (glucose polymers 5–500 molecules long), introduced by Chandra Mistry and Ram Gokal of Manchester, England in 1987 [52]. The size of the molecule was optimized in subsequent studies

and is now, as Icodextrin 7.5% (Baxter Laboratories), a feature of the clinical dialysis scene, especially for diabetics and those experiencing ultrafiltration failure using glucose solutions.

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23. In many countries of the developing world, CAPD did not develop because the cost of fluids produced in the industrialized countries was too high to permit its use. Importation of all fluids also meant that middle-men added further costs, such as in many South American countries. Local production of peritoneal dialysis fluid was discussed frequently with its low associated labour costs, but was rarely carried out even in large countries such as India, mainly because of fears by manufacturers that this fluid could be re-exported to developed countries at a lower price than the original product. In India also there has been a prejudice against using CAPD in a 'tropical' environment, with the untested suggestion that infections would be very frequent. In fact experience in Hong Kong (where CAPD was and is extensively used) showed this to be nonsense, and infection rates there were (for example) lower than in New Zealand, and CAPD is now expandng in India, although still used only on a tiny scale as with all dialysis modes of treatment. In Mexico over 90% of patients use CAPD as the preferred mode of treatment.
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39. Since CAPD is a equilibrium technique, clearly Kt/V_{urea} cannot be calculated from any fall in blood urea, or any other solute as in haemodialysis. Keshaviah and others have suggested that since $K = (V/t)\cdot(\mathrm{D/P})$ then $Kt = V\cdot(D/P)$ that is, the volume of dialysate drained (i.e. including ultrafiltrate) per unit of time (usually 24 hours) times the ratio of solute in dialysate to that in the plasma. This general equation can be applied to varieties and durations of dialysis whether continuous or intermittent. To this clearance must be added

residual renal function to give total Kt/V_{urea}, and the same problems and reservations arise and apply when measuring this as in haemodialysis patients (see Chapter 17, ref. [88]).

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Chapter 20

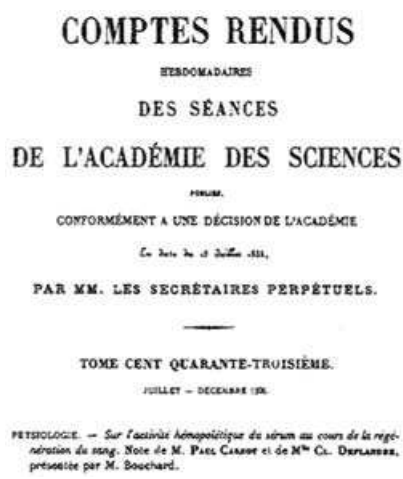
Good news and bad news: treatment of renal anaemia, the rising tide of diabetics with end-stage renal failure and withdrawal from dialysis

The treatment of renal anaemia

That anaemia was a regular feature of renal failure was, as we saw in Chapters 2 and 16, known from the work of Robert Christison in the 1830s [1] and a major problem in the early days of dialysis [2,3]. The 1980s saw a dramatic resolution of the problem, to the great benefit of patients on dialysis. Indeed one can argue that this has been the single most important advance in the treatment of chronic renal failure by dialysis since its inception in 1960.

The causes of anaemia in renal failure remained a subject of debate until a decade ago, as we have seen, and early studies such as those by Basil Rennie and his haematology colleague J. Markson in Glagow in 1956 [4] and Gabriel Richet and colleagues in Paris [5] in acute renal failure in 1954 seemed to favour a marrow unresponsiveness. Later work in the 1980s was to support this idea. However, some puzzling evidence pointed to a strong role for the kidney in protecting against anaemia. Thus, some patients with just as severe uraemia but a large renal mass (such as polycystic kidneys) could have near normal haemoglobin concentrations, whilst those whose kidneys had been removed were universally and desperately anaemic. The relative roles of deficient erythropoietin production, defective marrow response because of uraemic toxins and haemolysis were all considered during the 1960s and 1970s. At that time assays for erythropoietin were only just beginning (see below) and could not measure reduction in plasma concentrations, so that the inhibition hypothesis was generally favoured—although haemolysis clearly played a role as survival of infused cells labelled in one way or another, whether autologous or not, was reduced. Thus it was by no means clear that the hormone stimulating red cell production was crucial, or even important.

A hormone promoting the bone marrow to produce red cells had first been postulated in the nineteenth century from changes in haemoglobin in response to hypoxia at altitude (reviewed in refs 1,6,7]), and the plasma transfer done from anaemic to normal rabbits by Pierre Carnot (1876–1957) with his assistant Claudine Deflandre in Paris in 1900 [8], who called their putative hormone 'hématopoïétine' (Fig. 20.1). However, it had only a shadowy existence for almost half a century, as their



COMPTES RENDUS

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DES SÉANCES

DE L'ACADÉMIE DES SCIENCES

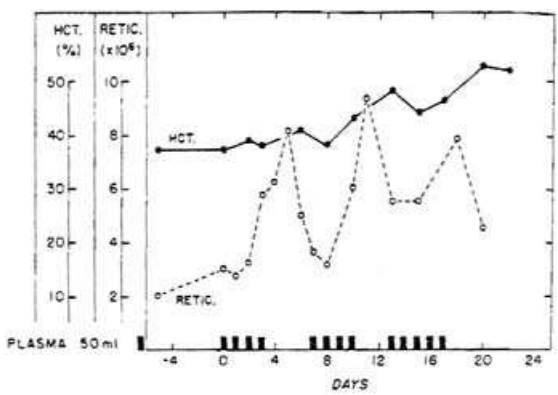
CONFORMÉMENT A UNE DÉCISION DE L'ACADÉMIE

PAR MM. LES SECRÉTAIRES PERPÉTUELS.

TOME CENT QUARANTE-TROISIÈME.

PHYSIOLOGIE. — *Sur l'activité hémopoïétique du sérum au cours de la régénération du sang.* Note de M. Paul Carnot et de Mlle Cl. Deflandre, présentée par M. Bouchard.

(a)



(b)

Fig. 20.1 (a) The first description of a haemopoietic principle in the blood by Carnot and Deflandre in 1906 [8]. (b) Only 50 years later, however, was this work finally confirmed by Alan Erslev [14] who showed that injection of plasma from anaemic rabbits into other animals could produce a reticulocytosis, and raise the haemoglobin concentration.

work could not be replicated by many other investigators [9]. Only in 1948 did it acquire its modern name from the work of Eva Bonsdorff and Eeva Jalävisto of Finland, who called it *erythropoietin* in recognition of the fact that it stimulated almost exclusively the red cell series [10]. Finally, definite evidence that it must exist came from work on parabiotic rats (joined together by surgery) of Kurt Reissmann (1912–1981), a German émigré from Schönbeck working in Kansas City in 1950: when one rat was bled, the other increased its concentration of haemoglobin and red cell count in response to something passing between them [11]. Additional evidence came from observations by astute clinicians on patients with a patent ductus arterio-

Fig. 20.2 Eugene Goldwasser, who worked on erythropoietin for more than 20 years, first prepared the purified hormone and made the recombinant product possible. (Courtesy Dr Chris Winearls.)

sus and reversed intracardiac shunts, so that blood with a low oxygen concentration perfused only the lower half of their body. However, the marrow in oxygenated regions such as the sternum was stimulated, clearly by some circulating agent [12,13]. Finally Alan Erslev (b. 1912), another émigré to the United States, this time from Copenhagen to Yale, managed to demonstrate without doubt in 1953 that plasma from anaemic rabbits contained an unknown substance which stimulated the bone marrow [14]. His experiments avoided the defects of previous studies, and he used much larger volumes of anaemic plasma than other workers in the field.

The subsequent history of erythropoietin in the modern era has been discussed by Goldwasser [15], Winearls [16] and Eschbach [17], all major players in the story. Only 4 years later in 1957, Leon Jacobsen and Eugene Goldwasser (Fig. 20.2) working in the University of Chicago identified, to their surprise, that the kidney was the source of the hormone [18]. The reason for the kidney to be the site for oxygen sensing and regulation of red cell production remains obscure even today. Assays using radioactive iron incorporation into hypoxic mice in a low oxygen chamber were developed [18], and in 1961 Gallagher and colleagues were able to show that there was a deficiency of erythropoietin in uraemic subjects [20] so that Joe Eschbach and Belding Scribner, who had invited him to work on the problem in Seattle, could point out in 1967 that the anaemia of uraemia was principally the result of erythropoietin deficiency and might be treatable using the hormone, if it were available [21]. Erythropoietin-rich plasma and urine extracts were in fact infused thereafter into uraemic patients by Ursula Essers [22] and others [23], but failed to produce a rise in haemoglobin or even in reticulocytes. However in experiments in uraemic sheep during the 1970s and early 1980s Joe Eschbach (b. 1933) (Fig. 20.3) and John Adamson [17] were able to

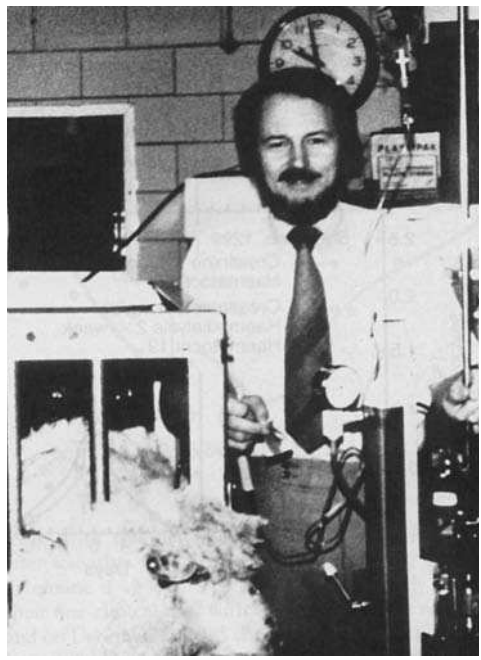


Fig. 20.3 Joe Eschbach (b. 1933), who first used recombinant erythropoietin in human subjects, treating one of his experimental uraemic anaemic sheep with erythropoietin-rich sheep plasma during the 1960s. (From [17] with permission. See Permissions.)

produce a marked response, and unlike previous work they were able to reproduce this in a single patient on dialysis using infused erythropoietin-rich plasma. Eschbach was thus able to predict with some confidence that when and if human hormone became available, it would be effective in treating the anaemia of uraemia.

But for clinical use, first the hormone had to be purified and prepared in useable quantities. Meanwhile, as outlined in Chapter 16, patients continued to suffer the consequences and sometimes the side effects of inadequate treatment of their often crippling anaemia. Blood transfusions, with all the risks of hepatitis and other infections known and unknown, disappeared more rapidly than in normal subjects, and left behind a patient with a growing and eventually toxic load of iron. Today it has become difficult for those patients and clinicians who did not experience this period up to the late 1980s to realize how awful life on dialysis could be, with a haemoglobin from 4–7 g/dL, that is less than half the normal amount.

Goldwasser, after 15 years of work, was finally able to purify erythropoietin from urine in 1976 [24]. He used urine because erythropoietin is present there in much higher concentrations than in plasma, because it is filtered at or near the glomerular filtration rate. Goldwasser was fortunate to be able to obtain 2550 L of urine from patients with aplastic anaemia in Kumamoto city, Japan, whose bone marrows could not respond to the enormous amounts of erythropoietin their kidneys produced in an attempt to correct the anaemia, which was excreted in their urine. From this huge

volume he extracted 8 mg of pure hormone, and showed this to be a highly glycosylated protein of 165 amino acids with a molecular weight of about 30 000 [24]. However, there was no way therapeutic amounts could be obtained in this fashion [25], and it was not until advances in molecular biology permitted the sequencing and cloning of the molecule that recombinant material became available. This was done by two independent groups in 1985 led by Fu-Kien Lin at the newly founded company, Applied Molecular Genetics or Amgen [26] and by Kenneth Jacobs and colleagues [27]. Given the complexity of the glycosylation (more than 30% of the molecular weight), an active molecule seemed unlikely. However, mammalian cells were used rather than the usual bacterial systems to cope with this problem, and the material worked! It was prepared for human use through the Amgen Corporation (now known as epoetin-alpha) and was injected for the first time into a human subject on 3 December 1985 by Joe Eschbach in Seattle [17], and a year later almost simultaneously reports from Chris Winearls (b. 1949) and Mary Cotes and their colleagues in Oxford, England [28] and the Seattle group [29] appeared in print describing the effects of the new material (Figs 20.4 and 20.5).

These results were little short of sensational. Until that time it was not clear just how much improvement the hormome would achieve, given that the differentiating cells in the bone marrow were still bathed in toxic uraemic plasma. It was immediately evident that the prime cause of uraemic anaemia was not inhibition of cells by uraemic toxins, but deficiency of erythropoietin. In 1988 the new hormone was licensed for clinical use and it appeared to be effective not only in all groups of

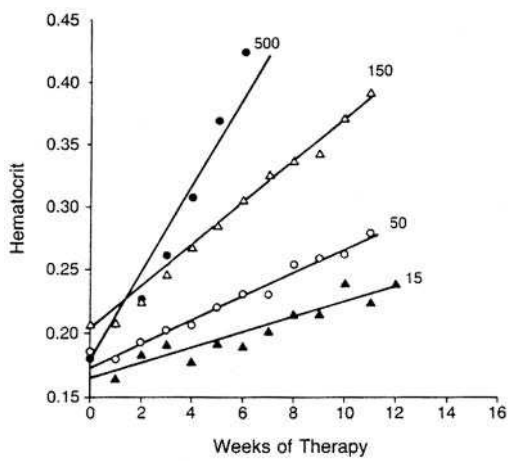


Figure 4. Slopes of the Rates of Increase in the Hematocrit in Patients on Dialysis Given Various Doses of Erythropoietin Three Times a Week.

The doses are expressed in units per kilogram of body weight. (Reprinted from Eschbach et al.[13] with the permission of the publisher.)

Fig. 20.4 The response of anaemic patients on dialysis to recombinant erythropoietin was nothing less than sensational. (From [29] with permission.)

Fig. 20.5 Similar results were obtained at the same time using recombinant erythropoietin for the anaemia of patients on dialysis by Chris Winearls, Mary Cotes and their colleagues in Oxford, England during 1986. Dr Winearls (left) is seen here with Dr Eschbach (right). (Courtesy Dr Chris Winearls.)

patients on dialysis of all ages including children, but also in those uraemic patients with severe impairment of renal function but not yet on dialysis. Dose ranges were established, and clinical trials involving hundreds of patients were rapidly organized using one of two clones available, alpha and beta [30–32]. Relatively few problems emerged even during the nervous first months and years of use, principally concerning a rise in blood pressure which still excites physiological interest and controversy. However, the overwhelming effect was one of enormously improved well-being in the patients, disproportionate it seemed to some observers to the modest rise in the patients' haemoglobin. It seemed that many deleterious effects attributed to uraemia could be overcome if the anaemia were even partially treated, without any change in the uraemic status—for example disorders of sexual dysfunction, cognitive cerebral function, sleep disorders and, of course, exercise tolerance. There was also a decline in known risk factors for cardiovascular events, in particular left ventricular hypertrophy.

There had to be a snag, and there was. This was the continued high cost of using recombinant erythropoietin [33]. Also, because the first patients treated were often those with the worst anaemia, their haemoglobin concentrations were raised only partly towards normal, especially as it was feared that their blood pressure might rise excessively. The higher the haemoglobin target set, the larger the dose of epoetin required and the higher the cost. Thus for both fiscal and medical reasons, the approach taken from the beginning was a curious and unprecedented 'bottom up' one of aiming only for partial correction of the haemoglobin concentration, with an effort to try and establish the *minimum amount* of hormone that could be used to produce major effects on the patients' lives [34,35]. An arbitrary target level of about 10 g/dL of haemoglobin was set very early on—still quite severe anaemia—but this low concentration was supported by an *ad hoc* committee of the National Kidney Foundation in the United States, and was widely adopted. An early and highly influential prospective randomized controlled trial was done in Canada [36], which showed clearly the advantages of a rise to this level, but seemed to show that achieving somewhat

higher concentrations of haemoglobin was not associated with further improvement in well-being or in physical performance. Moreover, neither this trial nor any subsequent or previous study had shown improved *survival* of patients with the rise in haemoglobin concentration. These results seemed counterintuitive, especially as repeated retrospective studies then and since showed repeatedly that those patients with the lowest haemoglobin concentrations had the highest mortality, and that cardiovascular risk factors such as left ventricular hypertrophy were moderated, although not reversed. Of course there were many confounding factors operating within such data. Discussions on the question of optimum haemoglobin centred, therefore, on effects on quality of life rather than survival, and in cash-limited dialysis programmes such as in the United Kingdom, on just how much the state was prepared to pay for better well-being without an evident increase in patient survival. Even in the United States, reimbursement was withheld for most of the 1990s for erythropoietin should a patient achieved a haematocrit higher than 36% (haemoglobin 11 g/dL)—still anaemia by any definition.

The alternative, more usual approach to a hormone deficiency such as hypothyroidism, that of routine total correction, only emerged in connection with epoetin therapy in 1993 when Joe Eschbach said what was in many people's minds by this time [37]—that the haemoglobin should be *fully corrected* to concentration ranges normal for age and sex, and that the 'minimum dose' debate was asking an inappropriate question. Since then, there has been a vivid debate on these issues, and several conflicting controlled trials (summarized in refs [34,35]). Evidence has accumulated over the past decade, however, in favour of the idea that at least in those without major cardiac problems, normalization of haemoglobin does, indeed, produce further increments in physical and mental performance and overall quality of life [38]. Whether or not this can be achieved without a penalty of complications remains a matter of dispute, especially in patients with cardiovascular disease [39]: the debate continues.

The rising tide of diabetic nephropathy

In 1969, the International Society of Nephrology held its fourth congress in Stockholm, and the International Diabetes Federation held its triennial meeting in Buenos Aires in 1970. In the whole of the programmes of invited and submitted papers at both of these meetings, there was not a single paper on the topic of diabetic nephropathy or renal failure in diabetes. It appeared that no-one in the world had anything to say on the subject.

Despite the prevalence (1–2% of total population in Caucasians, higher in many other groups) and the frequency of renal complications in diabetics, at the time when long-term dialysis began, diabetics with chronic renal failure were simply invisible. Diabetics rarely went into acute reversible renal failure in severe diabetic coma with ketoacidosis, perhaps because the osmotic diuresis of pre-coma arising from the massive glycosuria protected against the concomitant dehydration; more common as a cause was urinary sepsis, particularly with obstruction and papillary necrosis [40]. At that time, systemic disease generally was considered a contra-

indication to long-term dialysis or transplantation, and so diabetics were not considered. Thus there was little contact to begin with between those looking after diabetics and the new breed of nephrologists.

The history of diabetic nephropathy has never received a proper review, but Åge Chr. Thomsen of Copenhagen, in a landmark book on the subject, still worth reading today, gave the best available account of its history in 1965 [41]. There are also some details in the preface by Eberhard Ritz and Ivan Rychlík to their book [42]. That diabetics could suffer renal disease has long been known. Following the first description of proteinuria in diabetics by Domenico Cotugno in 1774, John Rollo (1798), perhaps Erasmus Darwin (1801), and certainly John Blackall (1814) and Richard Bright (1840) all described proteinuric diabetics, but it was Pierre Rayer who in 1840 established clearly that there was a diabetic form of Bright's disease with proteinuria and sometimes oedema [43], and even recognized that an increase in the size of the kidneys might occur. In retrospect, he must have seen mostly patients with maturity-onset type II diabetes (see below), since before the days of insulin (introduced only in 1923) no type I, young autoimmune diabetics would have survived long enough to develop renal complications. The studies of Griesinger in 1859 [44] and Ingerslev [45] in 1869, who both noted uraemia and death from this cause in diabetics, and of Bouchardat in 1883 [46], established the seriousness of the combination which had previously been thought to be benign; many were misled by transient albuminuria in diabetics severely ill from other causes. This was the case in van Noorden's large study of no less than 650 diabetics in 1912 [47], of whom 21% showed albuminuria which he thought benign, but even so he also observed patients with contracted kidneys, fundal changes, hypertension and uraemia.

The first histological studies recorded dealt only with tubular changes of fat deposition by Lionel Beale in 1853 and Theodor Frerichs in 1859, and of tubular glycogen deposits by Enrico Armanni in 1877. The first descriptions of glomerular changes date from 1883, when Stephen Mackenzie [48] described the glomerular arteriolar lesions so prominent in diabetic kidneys. Then in 1885, Inglessis [49] noted hypertrophied glomeruli with thickened capillary walls on safranin staining in a 57-year-old diabetic, and E. Strauss in 1887 noted in another oedematous 57-year-old 'irregular amorphous masses' in the glomeruli, which may be the first hint of nodular diabetic glomerulosclerosis. Curiously although the great German pathologist Theodor Fahr noted glomerular changes in diabetic kidneys, he attributed these to amyloid—which they can resemble closely. In 1928 an excellent paper by the Japanese Kinzo Waku described [50] the diffuse capillary lesion of diabetic nephropathy in 13 older patients with long-standing diabetes, and Bell [51] in the United States made similar brief but better-known observations. Only in 1936 did Paul Kimmelstiel (1900–1970) and the London physician Clifford Wilson (1906–1997), visiting on a Rockefeller scholarship, describe from the Boston City Hospital nodular nephropathy in post-mortems from eight patients, seven with maturity-onset diabetes, as well as the arteriolar, capillary capsular and tubular changes noted by others before them. They named this appearance '*intercapillary glomerulosclerosis*' [52]. Several other pathologists confirmed their findings, notably Arthur Allen of Downstate Hospital, Brooklyn in 1941 [53].

The first material from *renal biopsies* in diabetics was studied by Poul Iversen and Claus Brun in 1951 in Copenhagen [54], and then by Richard Joske in Melbourne [55] and Jean-Michel Suc [56] in Toulouse, France in 1954. A comprehensive account of biopsies from 53 patients with diabetic nephropathy was published by David Gellman and colleagues from Robert Kark's group in Chicago in 1959 [57] and also employed electron microscopy.

At this time the number of maturity-onset diabetics surviving to develop end-stage disease must have been rather small, although many will have died of vascular complications with reduced renal function. In contrast the number of younger diabetics surviving long term rose sharply after the introduction of insulin treatment in 1923. From what we know now about the timescale of diabetic nephropathy, it is clear that this will have led to a cohort of patients who went on to manifest renal disease 10 or 20 years later, and developed renal failure 20–30 years from onset—that is in the 1950s and 1960s. At that time about half of young insulin-requiring diabetics developed nephropathy (53% in the Steno study in Denmark) so the problem of renal failure was evident in the young. At that time Joslin [58], in a study of over 4000 diabetics over many years, was able to demonstrate that, in contrast to findings in the 1920s and 1930s (2% of 99 deaths), in the 1950s 63% of 119 deaths occurred later and were the result of renal failure. Thomsen's view of the treatment of diabetic renal failure in 1965 [41] was:

> the renal failure will progress in spite of all forms of therapy. In the terminal stage the physicians' role will mostly be of psychological nature, attempting to maintain a reasonable degree of optimism in the patient.

Although John Merrill is quoted on the treatment of renal failure, there is no mention of dialysis nor of transplantation. In 1963 Alexander Marble wrote in the earliest comprehensive American textbook on renal disease [59]: 'repeated dialyses in the presence of reduced kidney size and diffuse vascular disease serve only to delay the inevitable fatal outcome'.

The earliest report I have located on treatment of diabetic patients with chronic renal failure by dialysis is that of Morrell Michael Avram of Long Island Hspital, New York, in a single patient treated in New York and reported to a conference held in 1966 [60]; the following year Abella and colleagues published details of two more patients [61]. The fact that these individual case reports seemed worthy of record suggest the rarity of such treatment at that time. In the United Kingdom the first diabetic patient was placed on long-term dialysis in 1968 by Joanna Sheldon in Brighton [62], but the experience was never published. Even by the end of the 1960s, treatment of diabetics was rare: the University of Minnesota, however, were pioneers in this area of treatment, accepting diabetics for transplantation after prior haemodialysis from 1968 onwards [63].

This exclusion seemed justified at first in view of the gloomy outcome for patients on dialysis reported by several groups in the early 1970s. Thus only three decades ago as enthusiastic a worker as Kolff himself could write [64]:

> there is little prospect of improving the quality of life for patients with diabetic nephropathy and renal failure, and survival is likely to be short. For some we only prolonged the misery.

Not only was there gloom about ability to help diabetics, but the impression persisted that renal failure from diabetics was rare. For example, in the 1974 report of the registry of the European Dialysis and Transplant Association (EDTA), diabetes was not analysed separately, but was relegated to the section on 'rarer causes of primary renal disease'! Thus at the beginning of the 1970s, almost none of the few patients treated by long-term dialysis suffered from diabetes as a cause of their renal failure—0.5% in the 1970 report of the EDTA registry. Almost certainly they were never referred by their physicians, rather than being turned down for treatment. Only a few papers appeared on the subject [65] and in 1976 (the first year for which we have any detailed separate statistics for diabetics), only 3% of incident patients accepted on to renal failure programmes had diabetes in Europe. Only a few individuals realized the actual size of the problem [66], and this meeting (published in *Kidney International* in 1974) can be seen as a turning point, when the nephrology community began—but only began—to understand what they were facing in terms of specific problems and the sheer size of the population potentially involved [67]. As the 1980s began, Eli Friedman and his colleagues at Downstate Medical Center in Brooklyn, New York brought the problem forcefully and repeatedly to the attention of a rather reluctant nephrological community [68].

Major problems in the early days of haemodialysis in diabetics were haemorrhage into the eyes, so that a high proportion of patients who started on dialysis with sight lost it within a year or two [63,64], and difficulties with access [69] sometimes leading to gangrene. These problems made peritoneal dialysis an attractive alternative for the few patients then receiving treatment, from 1971 onwards [71–75]. Use of peritoneal dialysis in diabetics was patchy throughout Europe: in 1976 71% of Spanish diabetic patients in end-stage renal failure were taken on to intermittent peritoneal dialysis, whilst none at all were so treated in half a dozen countries, including Germany. In the United Kingdom the proportion was 54%. A pleasant surprise was the finding that control of the diabetes became easier in patients with 'brittle' diabetes using the addition of insulin to the dialysis fluid, although much larger amounts were needed than subcutaneously. This arises because the insulin is absorbed through the peritoneum during dialysis [75] and its delivery though the liver mimics the physiological route, and the constant supply of large amounts of both glucose and insulin 'clamps' the blood sugar effectively in most patients to effect an 'artificial pancreas' [76].

Thus when CAPD was introduced in 1978 (see Chapter 19), it was enthusiastically applied to patients with diabetes [77–79]. Even blind patients could be taught to use the technique without a penalty of higher infection rates—indeed, in several studies the infection rates in the meticulous blind diabetics was lower than that of their peers! I remember in 1981 our first blind diabetic patient proposed for CAPD. She cut short our discussion of how she might manage the technique with the remark that if she could prepare and serve a meal for her family on a gas stove without burning herself, she could surely manage CAPD procedures: and she did. As before, take-up of CAPD varied from country to country, the United Kingdom being particularly keen to use it for diabetics (51%, plus a further 31% on intermittent peritoneal dialysis in 1985 [79]), but almost everywhere a higher proportion of diabetics were started on CAPD than of those with other underlying diagnoses.

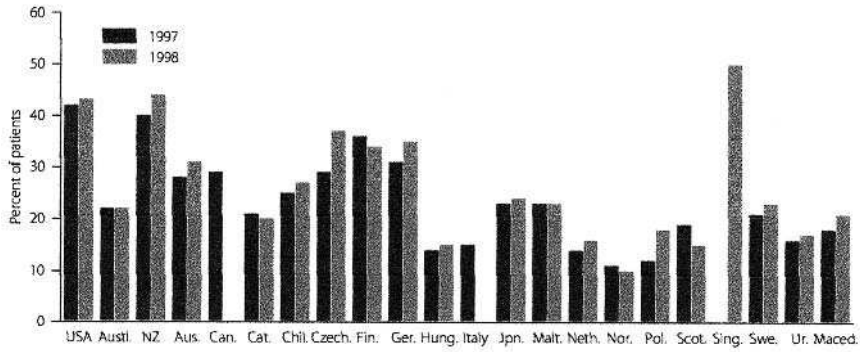


Fig. 20.6 The percentage of patients presenting for long-term dialysis as a result of diabetes mellitus in different countries in 1997 and 1998. The United States is far left, with New Zealand third from the left. The high proportion of diabetics in New Zealand arises principally from the Maori and other Polynesian populations in whom diabetes is particularly common. Other countries tend to show a lower proportion of renal failure resulting from diabetes, with Germany, Czechoslovakia and Finland having the highest incidence in Europe. The prevalent dialysis populations show lower percentages, but the proportion is rising in all countries. (Fom *USRDS report* 2000.)

During the remainder of the 1980s and the 1990s the main impact has been the sheer increase in numbers of patient with diabetes coming on to renal failure treatment, especially in the United States. In 1981, only 3% of patients in American dialysis units had diabetes: by 1985, 20% of the new intake was diabetic; by 1991 this was 34% and in 1998 it had risen to almost half (43%), with one in four (24%) current patients under treatment having diabetes [80]. All this was against a background of the huge increase in absolute numbers of patients (see Table 21.1). Similarly in Europe by 1980 the proportion of new intakes on to dialysis with diabetes had risen from 3% to 6.5%, by 1985 to 10.8% [79], and by 1993 to 17%. In the United Kingdom the proportion of new intake rose from 1.5 % in 1975 to 11% in 1985 [81] and is still slowly rising at around 18% nationally, with major regional variations according to the ethnic mix of the local population. Data from across the world in the mid 1990s illustrates the widespread nature of the problem (Fig. 20.6).

How has this enormous and potentially catastrophic change come about? [42,82] One question which arises immediately is whether diabetes itself has become commoner during the past two decades. Diabetes in both Europe and North America has become more common in this period [83,84], but because of the long induction period of 20–30 years from onset before renal failure supervenes this cannot yet have had an impact on numbers of those entering end-stage renal failure. Moreover, a lifestyle of inactivity and high calorie intake favours the development of maturity-onset diabetes in genetically susceptible individuals. The ageing of the population has exposed greater numbers of individuals to this risk, and the decreasing mortality from cardiovascular causes in older diabetics has resulted in more surviving, possibly to develop renal failure later. Genetic factors appear to be important, in that some ethnic

groups have a much higher incidence of both diabetes and diabetic nephropathy, particularly Afro-Americans and native Americans in the United States, Afro-Caribbeans in the Caribbean and Britain, South Asians and almost all Polynesian populations. In Germany there is a particularly high incidence of older diabetics in some regions, for example the lower Neckar region [42,82] where the proportion of new patients with diabetic end-stage renal disease is now above 50%of the total intake. But the most important factor may be simply that barriers to referral for treatment of their end-stage renal disease have broken down, especially for older diabetics. This happened earlier in the United States for reasons of law and reimubursement than in Europe, particularly in the United Kingdom [79] which initially lagged behind [85]. However, we must conclude finally that a 10-fold rise in numbers of older diabetics in renal failure over a decade is not fully explained by any or all of these factors.

The previous paragraph has touched on important subjects not yet discussed: the age of the patients and their *type of diabetes*. Age is easy to measure, and the diabetic population has 'greyed' even more dramatically than the dialysis population as a whole. The type of diabetes is not so easy to assess. Usually, diabetes has been divided on clinical criteria into two main groups: (i) a relatively homogenous group of *type I* diabetics with an abrupt onset at a young age (<30–40 years) of insulin-requiring diabetes, probably on the basis of an autoimmune attack on the insulin-releasing cells of the pancreatic islets; and (ii) a diverse group of disorders driving older patients slowly into insulin resistance and finally glucose intolerance, whose *type II* diabetes can in general be managed by diet or oral agents to stimulate insulin release. These patients are probably better managed with insulin at some points, for example to stabilize their diabetes initially, or during periods of stress such as infections. Therein lies the problem of defining 'insulin-requiring' or 'insulin-dependent' diabetes. Neither age nor a requirement for insulin easily defines the difference, which has resulted in the proportion of insulin-requiring diabetes being overestimated in most epidemiological studies, unless a detailed study of case records is made [86]. The problem is further compounded by the fact that a substantial proportion (perhaps 10% or even 20%) of older diabetics develop renal failure from causes other than their diabetes, such as vascular disease or coincident glomerulopathies. Nevertheless, the consensus is overwhelming that the great increase in diabetic renal failure in recent years worldwide has occurred amongst patients with type II (maturity-onset, generally non-insulin requiring) diabetes.

This was a surprise, since until recently it was thought that type II diabetics did not develop renal disease—only 5% of deaths were attributed to this cause in an influential paper of 1972 [87]. In contrast, as noted above, up to two-thirds of juvenile diabetics develop renal disease. The reason for this has been discussed already; although it was shown in 1989 that all types of diabetics developed renal disease at the same rate [88,89], until this decade older diabetics had simply not survived their vascular disease long enough to develop renal failure. Now, they were entering uraemia in greater and greater numbers, bearing the additional burden of their cardiac and vascular problems to contend with.

Despite the difficulties with definition, some striking differences between countries in the pattern of diabetics developing renal failure emerged during the 1980s. For

example in Scandinavian countries, a relatively low incidence of end-stage renal failure was almost exclusively in young, insulin-requiring patients. In Italy and France, in contrast, the population—again a relatively low incidence overall—is predominantly composed of older non-insulin requiring patients [75].

It is disturbing and disappointing to record that the outcome of treatment of all diabetics remained, and still remains, poor. On the other hand, this mortality has remained constant despite a progressive ageing of the incident and prevalent dialysis population, which might be considered a (modest) achievement. Over the years there has been a contrast between remarkably good results published from a few centres, and the overall much poorer results from comprehensive regional and national registry studies. Almost certainly this can be explained by the strong process of selection whereby the 'best' patients are diverted to what is perceived to be the treatment of choice, usually transplantation. For example, in Minneapolis the excellent results of transplantation of diabetics there are world renowned [90]. Less often cited are their understandably poor results of the remainder of their patients who were treated only by dialysis [91]; all patients of all ages treated only by dialysis were dead within 7 years of starting treatment.

In 1980, the EDTA registry reported the first large-scale outcome study: only 34% of diabetics on dialysis in Europe survived more than 3 years, and even in the 1990s *every* large international, national or major regional registry continued to report a 50% survival period (half-life) of only between 2 and 4.5 years for all diabetics (weighted mean about 3.3 years), with an annual mortality of around 25–30%. This is worse than that for non-diabetics even when corrected for factors such as age. Fewer than 4% of diabetic patients of any age survive more than 10 years on dialysis in the United States [80] and surely European data today would be no different. There is surprisingly little gradient with increasing age, although older patients as might be expected do a little worse. This high early mortality arises principally from the burden of cardiovascular disease that the diabetic population carries, and sepsis also plays a role. Finally and sadly, withdrawal from dialysis (see below) is a major source of death in diabetics, brought about by overwhelming physical problems and poor quality of life.

Prevention at last?

One ray of hope appeared during the 1990s to counter all this gloom: the possibility of averting or preventing the appearance of renal damage and renal failure in diabetic patients. The Steno study in Denmark had shown a steady fall in the proportion of young type I diabetics developing renal disease, from 52% in the 1950s to only 33% in the 1980s [92]. The suspicion was that, factored by genetic background, the quality of control of the diabetes might be the most important factor in this. This was shown to be possible in major collaborative prospective controlled trials, first for type I diabetics [93], and later for type II diabetes [94]. In addition, treatment with hypotensive agents of the angiotensin converting enzyme (ACE) inhibitor class, even in those with normal blood pressures, is able to slow and prevent the appearance of renal damage even in those with normal blood pressure [95]. The goal of prevention of diabetic renal complications is, if not a fact, at least in sight.

Suicide during dialysis and withdrawal from dialysis

Within only a few years of the beginnings of long-term dialysis in highly selected, young (and generally resilient) patients, the fact that a number desired to withdraw from treatment and a few actively committed suicide became evident. Both Scribner and Schreiner commented on this in 1964 and 1965 [96]. The stresses of a life prolonged by dialysis were known to be considerable, and patients had easy access to means of self-destruction as well as simple discontinuation of the procedure. During this early period the occurrence of suicide in a dialysis patient either actively, or passively by uraemia from cessation of dialysis, was almost always against the wishes of the medical attendants and without their co-operation, and was perceived by them both as defeat and loss and the result of temporary—and it was hoped treatable—episodes of profound depression. A survey of US units in 1971 by Abrams, Westervelt and their colleagues of 3500 American patients (almost all of the prevalent population in that year) suggested an incidence of suicide in dialysis patients 400 times that of the general American population [97].

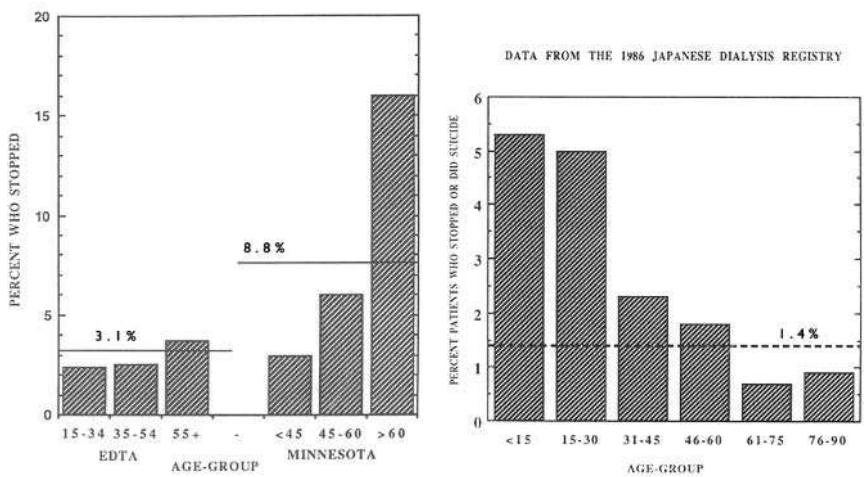
A similar survey in Switzerland 10 years later [98] noted a lower incidence of suicide (10/574 deaths from 1965 to 1978), and suicide continued into the 1990s as the cause of about 0.5–1% of deaths of patients on dialysis. However, in this study from 1983 a greater proportion of deaths (16/574) arose from 'refusal of further therapy'; together these categories were 25 times more common than in the general Swiss population. This appearance of a new phenomenon, *discontinuation of dialysis*, as a cause of death almost certainly arose from the fact that during the 1970s the dialysis population changed, became older, more damaged and more vulnerable. The idea that sometimes it might be appropriate to co-operate with the patient in their desire to stop dialysis treatment spread gradually during the 1980s, even though this went against many deeply entrenched medical, societal and religious attitudes [99]. The earliest paper I can identify which explicitly discusses the topic dates from 1981 [100].

In parallel remained the idea, present since the committee in Seattle in 1962, that some patients could be judged from the beginning to be 'unsuitable' for dialysis and denied this treatment. As discussed in Chapter 16, concepts of 'suitability' changed rapidly during the 1960s and 1970s, and were rolled back to include much more marginal patients. In ethical terms the two problems were linked, and since then often have been discussed together [89,101]. In the United Kingdom and most other countries, tacit or overt rationing of dialysis treatment was built in from the beginning: only the United States, having started with statements of a clear need for rationing, deliberately attempted to abandon the idea altogether.

In that country the 1972 legislation (see Chapter 21) has enshrined the right of anyone to dialysis treatment, should they require it, of whatever age. Thus it was in the United States that ethical issues surrounding withdrawal of dialysis arose earliest and in quantity, although some of the earliest papers came from Canada. The topic was brought into focus in 1986–1987 by several articles [101,102], the most comprehensive of which achieved international attention, that published by S. Neu and Carl Kjellstrand [101] in Minnesota. They described 704 patients on dialysis who died between 1966 and 1983, of whom 155 died from dialysis being stopped 'before a

biological cause of death supervened' and wrote further about the problem in numerous papers over the next few years. Dialysis was not, of course, the only field in which this type of question arose; as technology advanced, during the same decade similar ethical and practical debates developed in parallel about other life-supporting treatments, such as parenteral nutrition in long-term coma, support of very premature babies, life support and resuscitation in the elderly, and the withdrawal of cardiorespiratory support in acutely ill patients in intensive care units, all of which debates remain current [103].

By the end of the 1980s even though the practical definition and identification of 'withdrawal' remained considerable, withdrawal from dialysis had emerged—and still remains—a major cause of death in most dialysis units, behind only cardiovascular causes and vying with infections as the second most frequent cause. Problems with definition and allocation may account in part for the major differences between-dialysis units and countries as to what proportion of deaths are attributed to withdrawal of, or from, dialysis. These figures have remained highest in North America, intermediate in Europe and lowest in Japan (Fig. 20.7). Nevertheless, these methodological difficulties probably blur only a little major cultural and national differences, such as the *decrease* with age in cessation of dialysis in Japan [104], in contrast to the *increase* with age seen in all other countries for which we have data (Fig. 20.7). This fascinating finding almost certainly reflects attitudes to the elderly, and to being old in



(a) (b)

Fig. 20.7 The effect of cultural factors on the incidence and reporting of deaths attributed to withdrawal from dialysis. (a) Data from Michigan, MN and Europe (EDTA), and (c) data from Japan. Opposite patterns in the relation to the age of those on dialysis and the likelihood of withdrawal are evident. Note also the different frequency of reported withdrawals/suicides (8.8% Michigan, 3.1% Europe, 1.4% Japan). (From Kjellstrand CM. Practical aspects of stopping dialysis and cultural differences. In: Kjellstrand CM, Dossetor JB, eds. *Ethical problems in dialysis and transplantation.* Kluwer Academic, Dordrecht, 1992: 106–116, with permission.)

Japan as compared with the West. In the past decade discussion of the topic has been intense from practical, ethical, sociological and religious viewpoints [104–110], and now that elderly patients are the main dialysis population throughout the industrialized world (see Chapter 21), papers have come from many countries on the subject including the United Kingdom [110].

Finally, two main clinical problems can be identified: patients in whom issues of discontinuation arise but who remain competent, and can enter fully into discussion of their future; and patients who progressively become demented, often suffering a period of intermittent lucency in which their plight may be fully apparent to them. In the latter the presence or absence of any stated wishes ('living wills') may be crucial. The appropriate and compassionate management of such patients remains a major challenge to those caring for people in renal failure.

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Chapter 21

The growth of dialysis for long-term renal failure in its fiscal and sociopolitical context

A major part of the recent history of dialysis arises from the social, ethical and political problems that long-term dialysis treatment precipitated during the 1960s and subsequently. Never before had there been a life-saving treatment which was both successful, but repetitively and cumulatively expensive to the point where it seemed that society could not afford to treat all who might benefit. A full discussion of these ethical and sociopolitical issues (which remain with us, albeit with different boundaries) would require another book, and has already generated several major reviews [1–4].

The first impact was felt in Seattle when the success of the treatment for the fatal disease of terminal uraemia became known: there was an immediate overwhelming demand, even though from the beginning Scribner and his colleagues agreed only to treat patients from their immediate locality. Medical constraints were quickly put in place without (so far as one can see in retrospect) any real discussion, even though today almost all would be regarded as untenable: for example, an age limit of 45 years was effectively in place, diabetics were rarely if ever dialysed, and for almost a decade very few children less than 15 years of age were treated anywhere; hypertension was initially considered by many (including in Seattle) as an absolute contraindication to treatment by long-term dialysis!

Much more contentious was the attempt to deal with the ethical problem of rationing by attempting to evaluate the social needs and worth of potential candidates for dialysis using a panel of individuals drawn from various parts of society [5]. This 'jury' functioned in Seattle for 3 years, and began a debate which helped map the new territory of bioethics—indeed the dialysis experience can be said to have begun this area of study [6]. The issues were very complex, raising not only ideas of right, equality and fairness, but also a new debate which concerned a new measure of outcome: 'quality of life', which had until that time not been addressed in any other area of medicine in detail [7]. In addition there was a commitment until the death of the patient and no-one knew how long patients could or would survive under regular dialysis treatment. However, as Cheng [8] has pointed out:

> During the 1960s … articles in the media … focused on the agony of choice, rather than the agony of treatment. The distinction between surviving and living was overshadowed by the choice between living and dying.

Moreover, it was not clear in the mid 1960s which of peritoneal dialysis, haemodialysis or transplantation would prove successful—at that time only living related donor transplantation had shown any useful outcome, and overall results with dialysis were much superior to those of cadaver transplantation in terms of survival.

Imperceptibly at the time, the advent of a group of patients whose lives were maintained through long-term dialysis marked a radical change in the definitions and perception of disease, and created a need for health providers to alter their methods of management. This process of change had begun much earlier in a gentle fashion, when thyroid extract was introduced for hypothyroidism (by Murray in 1891) and then insulin for the treatment of diabetes (by Banting, Macleod and Best in 1923). Until that time, almost all medical contacts were brief and single: people judged themselves to be ill, sought the advice of a doctor who prescribed and carried out treatment. The patient either got better or, in the days before antibiotics or many other specific treatments, often died. Sometimes the course might be prolonged and relapsing, such as in tuberculosis—a model of things to come.

Now there were people whose disease required continued intense and unending support and management. Repeated consultations were necessary, and the patient's detailed involvement in his or her own care was crucial. A new contract between doctor and patient was needed, for which the only precedent was the management of diabetes, but with a much less intense involvement of either partner. This remained a fairly low-key activity, until it was raised to an altogether different plane by the introduction of regular haemodialysis: here the long-term contract was only too obvious, with no escape either for the patient of the caring staff until the patient died, or the carers retired or perished themselves. Health administrators had to face the novel prospect that each year and every year, a new cohort of patients requiring treatment and generating costs would be added to those already under treatment, so that even at a constant provision of services, staff and equipment requirements and hence costs would rise steadily until entry rates were matched by exits from the death of patients. This apparently simple point led to years of incomprehension amongst medical and fiscal administrators, simply because of its radical nature. Since those taken on for treatment were in general young in the early years of dialysis, this equilibration process has still not reached its final state 40 years from the start of regular dialysis treatment, and numbers under treatment continue to rise worldwide, albeit a little more slowly in the twenty-first century. For some time, models of dialysis growth have predicted equilibrium only in about 2010–2015—if then. The importance of this framework was that a new pattern of managing patients for the rest of their lives became a dominant theme of medicine in developed countries during subsequent decades, overwhelming, in terms of demand, the 'one-shot' consultation and treatment of brief illness, especially amongst the elderly. A subsidiary effect was that needs and patterns of care in the developed and the developing worlds drifted apart.

The perception of, and reaction to, the need for instituting programmes for the treatment of sufferers from terminal uraemia necessarily differed from country to country within the developed world depending upon the structure of the health care system (see Chapter 22), political and medical attitudes, even geography—not to

mention the problems generated in developing countries which did not possess even adequate basic medical facilities. In the third world, in many countries the demand for such expensive new hospital- and technology-based treatments distorted the health services away from less glamorous but much more necessary and cost-effective preventative medicine [9–12].

It is useful to examine the events in the development of renal failure services in two countries which illustrate widely differing approaches to the many dilemmas posed by the introduction of long-term dialysis: the United States and the United Kingdom.

The United States

In the United States [8,13,14] a health care system based largely upon private insurance was in place in the 1960s, although Medicare and Medicaid were available for certain minority groups such as the elderly, and a few other groups (e.g. veterans of military service). There was no clear point of responsibility, either fiscally or organizationally, from which programmes of treatment for 'new' conditions such as end-stage renal failure might be initiated.

In response to the introduction of long-term dialysis, as early as 1963 a conference attended by physicians, lawyers, ethicists and economists was convened jointly by the American Medical Association and National Kidney Foundation. This group [15] recommended a national budget for this treatment, but only at a level of 5% or less of the total cost, to establish training centres; who would pay for the remainder of the treatment itself was unclear. This general attitude remained the norm for the next few years: the costs of dialysis, both per patient and in aggregate seemed high and almost without any upper limit, even allowing for developments such as cheaper machinery and home dialysis to reduce costs. The issues were very complex, raising ideas on quality of life—a relatively new concept in itself [7]—plus a new commitment which would last until the death of the patient. The first of many estimates of how many patients would need treatment was made: 2000 per year, based on careful screening of patients using criteria similar to those used in Seattle. An estimate of total demand from which these lucky few would be selected was about 25 000. Thus it is often forgotten that dialysis began in the United States with as clear an intention to ration the treatment as it did in the United Kingdom, perhaps because the idea rapidly proved to be inapplicable with changes in the law and in practice, as well as almost certainly unethical.

Scribner approached the Department of Health and Welfare in Washington in 1963 with the idea that they should fund dialysis, at the enormous cost of $20 000 per year(1960 prices)—probably more than $100 000 in today's money. Not surprisingly, there was a negative response. They did, however, allocate $1 million to the National Institute of Arthritis and Metabolic Diseases (NIAMD) budget for research into the artificial kidney. Thus support was forthcoming from the National Institutes of Health for development research and in fostering this programme the role of Dr Benjamin Burton was important. Under his direction later studies into diafiltration, kinetic modelling, hollow-fibre dialysers and dialysis access, as well as oral sorbents for treatment of uraemia, were fostered by his Artificial Kidney/Chronic Uremia Program, begun in 1966.

Taking advice from the director of the National Institutes of Health Jim Shannon (himself a leading renal physiologist), the Bureau of the Budget set up a special committee in 1966 to report on the problem. It is interesting that they chose a physiologist, Carl Gottschalk (1922–1997), as the chairman of the committee, who had no experience whatsoever of the treatment of uraemia, perhaps because of his reputation for integrity and fairness, and thus would not be a member of any pressure group involved in the process. As a result the report [16] became familiarly known as the 'Gottschalk report', and had a major influence on thinking about the need for dialysis. However the committee did not suggest what the Bureau of Budget wanted to hear: the Gottschalk committee recommended that dialysis should be freely available to those who needed it on medical grounds; only 100 copies of the report were published, on a holiday weekend, and it was shelved. A second group was chaired by Burton, and reported to the Public Health Service [17]. This recommended that a mix of research and prevention should be considered as well as treatment.

Nevertheless a number of individuals and organizations, in particular George Schreiner of Georgetown and E. Lovell Becker (1921–1989) of Cornell as successive presidents of the National Kidney Foundation, continued to lobby on behalf of treatment for end-stage renal disease (ESRD) by haemodialysis, peritoneal dialysis, transplantation or whatever means were needed and available [8,13,14]. Patients, their relatives and doctors wrote to their congressmen, a patient dialysed himself before a session of the House Ways and Means committee. Results showing what could be achieved using regular dialysis were published in 1969 (87% 1-year survival and 58% 7-year survival) [18] which convinced many sceptics that useful life could indeed be prolonged.

Amazingly, on 30 October 1972 public law 92-603 was passed by Congress as an amendment to the Medicare act with only a single dissenting vote and after only 30 minutes' debate: the Senate followed with a 52–3 vote, and the bill was signed into law by President Nixon. This gave all American citizens the right to treatment for end-stage renal failure regardless of age—the only medical condition, before or since, to be given this status. The budget for this activity was to be located within the government's existing Medicare/Medicaid system. Thus we had the paradox that in a country with no comprehensive health care system for the majority of its citizens, end-stage renal failure became the unique responsibility of the federal government, with an open-ended budget.

Contemporary estimates of how many patients would eventually need treatment in the United States varied from 16 000 (a figure actually achieved as early as 1974) to 55 000; in fact by 1999 the total approached a quarter of a million! (Table 21.1 and Fig. 21.1) Therein lies the root of the continuing debate on the costs of the ESRD programme in the United States: no-one foresaw the giant number of patients that would be involved [19]. The annual budget was expected to be $250 million; by 2000 it was more than $15 billion, but virtually all patients who could benefit were receiving treatment—and, in the opinion of many, a number who would only suffer from intervention (see Chapters 20 and 22). One major factor in the underestimates of patients who might need dialysis was the lack of information on the high incidence of end-stage renal failure in the black population. The first hint in the late 1970s [20]

Table 21.1 Number of patients on dialysis in the United States

	Haemodialysis		Peritoneal dialysis		
	Home (%)	Centre (%)	Intermittent (%)	CAPD/CCPD (%)	Total
1960	–	100	–	–	5
1965	?	?	?	–	150e
1970	42	57.7	0.3e	–	2 508
1975	28	70.5	0.5e	–	13 300
1980	12.5	76	2.5	9	55 000
1985	7	78	2.5	12.5	83 000
1990	2.3	80.7	0.4	13.4	128 674
1995	2.	78.4	0.3	13.5	165 707
1997	1.5	80.0	0.1	12.0	224 022
1998	1.3	84.8	0.1	10.2	245 910
1999	1.3	89.0	0.1	9.5	253 581

CAPD/CCPD, continuous ambulatory cycling peritoneal dialysis; e, estimate.

Note that:

(a) the percentage totals do not add up to 100%, because in a small proportion of cases the type of dialysis is not known;

(b) although the *proportion* of patients doing home haemodialysis fell steadily from a peak around 1970, the *absolute numbers* using this form of treatment went on rising until the late 1980s, when it topped out around 6500 prevalent patients. In 1998, only 3100 patients were doing home haemodialysis;

(c) again although the *proportion* of patients doing CAPD (or CCPD) at home has remained fairly steady for 15 years, the *absolute number* peaked in 1997 at 26 640, falling back slightly in 1998;

(d) in addition to the above figures, in 1998, 100 543 and in 1999 97 739, Americans had a functioning allografted kidney, making a total on ESRD treatment of 346 453 (1281 pmp); the figures for 1990 were 52 312 and 180 896;

(e) haemofiltration is not available for state reimbursement in the United States for ESRD, and thus only a very few patients have been so treated in experimental programmes.

Detailed data from 1989–1999 inclusive from the USRDS can be obtained from their website www.usrds.org

was from R.E. Easterling who examined the population in the Delaware valley, followed by a study in Michigan, but it was not until the data of Stephen Rostand and his colleagues from Jefferson County, Alabama were published in 1982 [21], that this large incidence became widely recognized. These data confirmed a fivefold higher incidence of ESRD in Afro-Americans compared with local Caucasians, mainly from hypertension and diabetes.

The story of the 30 years from 1972 to the present was one of attempts by the Federal government to contain these escalating costs, whilst still providing the comprehensive treatment the law mandates. The high costs of end-stage renal failure treatment mirrored the general picture of health care in the United States, of high expenditure on health (today it is over 15% of gross domestic product) and low efficiency (up to 25% overheads, most to insurance companies but also substantial amounts to medical attendants).

(a)

(b)

Fig. 21.1 The growth of treatment by dialysis throughout the world from 1978 onwards. (a) Incidence of new patients per million population (pmp) per year, (b) prevalence on dialysis (note these prevalence figures do *not* include patients bearing successful transplant). (From [49] with permission).

The discussion of the 'dialysis problem' which arose out of these numbers was perhaps inevitably confused and involved several strands of argument: first, the unexpectedly large numbers—should all be treated? Second, the philosophy of how best to perform dialysis, with issues of home versus centre dialysis as a prime theme. Finally, how best and most economically to deliver the dialysis, through non-profit or for-profit providers. In fact the rapid 'privatization' of dialysis in the United States can be seen simply as a consequence of the health delivery system already in place, itself a by-product of the market philosophy traditional in the country [19] (see Chapter 22 for further discussion). Privatization began in the late 1960s with the formation of the National Medical Care Corporation by Constantine Hampers and Edward Hager in Boston in 1968, and gained considerable momentum after the passage of law 92–603 in 1972 guaranteeing treatment for ESRD. Its principal innovation was the idea of free-standing, out-of-hospital dialysis units specifically—and solely—geared to provide long-term dialysis. By 1980, 12 years after its foundation, this remarkably successful company provided dialysis for 23 000 patients (36% of the national dialysis population), principally in free-standing, out-of-hospital units [22], at a time

when the prevalent dialysis population of the United States was 63 000 in just over 1000 dialysis facilities. At that time the total American health care expenditure was $273 billion, representing already 9.4% of the gross national product (GNP), whilst end-stage renal failure costs were $1.2 billion, principally for dialysis, representing only 0.4% of the total health spend. However, these costs initially consumed one-quarter of the total Medicare/Medicaid budget, the only part of the budget directly accessible to government control.

Of course these figures were uncorrected for inflation, which in the case of medical supplies greatly exceeds the usual indices used to calculate comparative values, but even so seemed to the government administrators of the day an overwhelming—indeed impossible—commitment. The 'simple' facts of continuing expenditure on prevalent patients, plus increasing intake of a needy population much larger than any current estimates, quite eluded them. However, during the 1970s the costs of dialysis, corrected even for general rather than medical inflation, more than halved; it was the huge increase in patient numbers that fuelled the idea of a major cost over-run in the Medicare budget. Despite this apparent enormous expenditure, in 1981 it was evident [23] that treatment was available only in a very patchy way throughout the United States, immediately suggesting a large unmet need—which was to prove correct.

At the beginning of the 1970s almost all dialysis facilities were within university or community hospitals, and repayments for those eligible were geared to the overheads of hospital-based dialysis. At the beginning an important decision was taken to fund the system on a per dialysis basis, making remuneration sensitive to activity, and a figure of $174 per dialysis was set based on in-hospital costs. A lower figure, however, was reimbursed for out-of-hospital dialysis ($150), aimed at self-dialysis in the home, but included some out-of-hospital centre dialysis. Throughout the 1970s and early 1980s a running debate continued on whether the costs (and by implication profits) of this treatment modality were excessive, and creative accountancy allowed both sides of the argument to argue persuasively that their form of treatment was cheaper. Locked into this was the debate as to what role home self-dialysis (or aide-assisted dialysis), generally agreed to be cheaper, could or should play in the changing dialysis population, and what the outcomes of the dissimilar patients placed on either treatment might be. The passion of this prolonged discussion is clear from the texts and anecdotes which survive; in retrospect, however, it is apparent that those advocating for-profit dialysis on the one hand and in-hospital or not-for-profit home dialysis on the other were acting in a self-interested way, fuelled by their philosophy of health care rather than by the facts.

Whatever the rights and wrongs of the argument, already by the end of the 1970s, for-profit dialysis facilities accounted for a steadily increasing proportion—over one-third—of dialysis provision nationwide. The proportion has continued to increase steadily and now accounts for more than three-quarters of Americans receiving dialysis. The legal right to treatment with a fee available per treatment, underwritten directly or indirectly by the government, and the increasing population of uraemics as the population aged and the prevalence of diabetes rose meant that an ever-growing market niche was available in the form of dialysis. Many took the opportunity to enter this market and trade: a broad variety of facilities arose, from completely free-

standing isolated for-profit dialysis-only units to those still integrated within the old university departments of nephrology and medicine—but generating profits for the institutions and in many cases for the investigators themselves, as well as for the 'dialysis buccaneers'. Faced with rocketing, unprecedented and—to the government accountants at least—unexpected costs for the dialysis programme, successive US administrations have reduced the per dialysis fee in an attempt to contain expenditure, to $138 and then down to its current level of $126. In general, however, they adopted the passive and less publicly controversial role of simply allowing inflation to erode the real purchasing value of the per dialysis fee, now to only one-third or less of its original purchasing power. Even so, the total national costs of dialysis in America continued to increase. During the 1980s this put all dialysis providers, but especially those in the for-profit sector, under intense pressure to reduce costs, but not necessarily to provide the most cost-effective treatment.

The huge advantage of this 'dialysis market', however, was that the American people, in contrast to those in almost all other countries, were allowed with great rapidity comprehensive and unquestioned access to treatment [24]. In the great majority of cases treatment consisted of dialysis rather than transplantation, which despite expansion during the 1970s and 1980s remained constrained by a shortage of available organs (see Chapter 22). The many dangers of the market approach to dialysis development and delivery were—and remain—obvious. The needs of patients conflicted at many points with the efficient use of capital, staff and plant in dialysis units and, especially in areas of practice where hard data were absent, the tendency may have often been to go for the cheaper, rather than possibly the most cost-effective, choices. Whether this has resulted in practices which disadvantaged or even harmed patients or not is still under debate. Several sets of data [25–28] suggest that American patients treated in for-profit facilities receive less dialysis and less erythropoietin, are looked after by fewer staff, survive less well, and are less often referred for transplantation than those treated in non-profit facilities; some would argue that the only question is what the size of these differences may be. It comes as no surprise that these data are vigorously contested by those involved in the for-profit dialysis sector [22,28] who argue that they are treating an older, sicker, more fragile population who have not been referred for transplantation for these very reasons. Certainly in their favour it can be pointed out that the mortality of the prevalent American dialysis patients has fallen steadily during the past decade (in parallel with increased prescription and delivery of dialysis), during which time the proportion of patients dialysing within for-profit facilities has increased even further, to more than three-quarters of the prevalent population.

Undoubtedly these fiscal and commercial pressures helped, alongside patient preference and the availability of more powerful dialysers, to promote a drive to shorten dialysis hours and thus treat more patients per dialysis station, on which costs are fixed. Certainly the practice of reuse of disposable dialysers, in general marketed by their manufacturers as 'for single use only', has been entirely driven by economic constraints—although biocompatibility advantages have been described after the first use, perhaps arising from coating of the dialyser membranes with the patient's own proteins at first use. Gradually during the 1980s it was noted that mortality amongst

the US dialysis population had risen from the 14–15% per annum regularly reported during the 1970s and early 1980s to 23–25%, or even more. This was particularly high by international standards even when carefully corrected [29], and led to an examination of the possible causes of these poor outcomes, and in turn to the possible role of commercial pressures on dialysis quality. This led to an important initiative in 1989, a conference in Dallas in 1989 organized by Tom Parker and Alan Hull [30] on the whole subject of the high mortality in the American dialysis programme. This was one of the events leading to the formulation of a series of quality guidelines for the performance of dialysis by the National Kidney Foundation from 1995 onwards, as far as rather inadequate methodology of data analysis permit. In turn, this effort was aided greatly by two sets of important data. Historically, the first was the bank of patient data and outcomes started by National Medical Care in the 1970s and now maintained by Fresenius after its takeover of the corporation in 1996. The second and the major source was the re-emergence of a national ESRD data base in the form of the US Renal Data Service (USRDS) in 1989. Both groups have published valuable retrospective data analyses during the past decade, as well as collecting prospective data nationally, and in the case of Fresenius Medical Care, internationally.

Data are not yet available from the USRDS for 2000, but at the end of 1999 [31] intake on to dialysis was 88 091 (315 patients per million population (pmp) per year a figure only slightly higher than the previous year) and there were 245 910 Americans receiving dialysis (909 pmp), 77% of whom were dialysing in for-profit facilities; 66 964 deaths were noted during the year, and during 1998 an additional 22 000 patients came under treatment. Equilibrium is not yet evident, although the rate of increase is now slower. Total national health expenditure was around $1.2 trillion, 14.2% of the GNP (projected to rise to 15.1% by 2000), of which $17.9 billion was spent on ESRD ($12.7 billion through Medicare), that is about 1.2% of the total health spend. Overall annual costs per dialysis patient today are approximately $50 000 per patient for non-diabetics, and $10 000 greater for the increasing proportion of diabetics. However, it must be noted first that these data represent a steady fall in the absolute cost of dialysis, when corrected for inflation, ever since the 1970s ($126 in 2000 is equivalent to about $45 in 1975). Secondly, that the proportion of health spend on ESRD in the United States is no larger than that in other industrialized countries (see Fig. 22.5) [32]—it is the *absolute and proportional amount spent on health care* which is much larger in the United States than other countries, and this generally higher expenditure on health is reflected in the costs of the ESRD programme. Why should we expect dialysis to be any cheaper than other medical procedures in the United States? The problem—and there certainly is a problem—is a structural one which permeates the whole health delivery system of that country.

The United Kingdom

In contrast, in the United Kingdom, health care had been provided since 1948 (for the 98% of the population who chose to use it), through an integrated National Health Service (NHS) designed largely by Lord Beveridge in the dark days of 1942 during the worst of the Second World War. Its implementation in 1948 was a major plank in the

social programme of the Labour government of the day, and was masterminded into place by a tough—if not ruthless—politician with a clear social vision, Aneurin Bevan. Despite its many obvious and less obvious failings, the NHS has commanded the affection and respect of the great majority of the British population for more than half a century. Perhaps this is because above all it covers everyone without exception from cradle to grave, is aimed to be comprehensive in terms of treatment both emergency and long-term, and above all is free at the point of need. In practice, however, in the 1960s there was great variation in local provision and standards in many areas of medicine, which has diminished but by no means disappeared during the subsequent three decades. Even so, responsibility for the provision of funding dialysis was quite clear: it lay with the government, from general taxation and executed through the Department (then the Ministry) of Health. This structure was in line with the basic social philosophies held by the British people, particularly in the decades immediately after the Second World War (see Chapter 22 for further discussion).

Pioneers such as Stanley Shaldon (b. 1931) and Hugh de Wardener (b. 1916) had shown that long-term dialysis could successfully be applied in the United Kingdom in 1962–1964. However, an un-signed editorial in the Lancet of May 1962 [33], after reviewing progress, ended with the statement: 'Our limited resources should not be squandered on "mass-dialysis" for all suitable patients with irreversible renal failure if this involves curtailing treatment of frankly reversible lesions'. Already the possibility of deliberate overt rationing, or limiting the availability of the new treatment, was raised—a new concept in the delivery of medicine, which had greater publicity in the United Kingdom than in the United States even though to begin with it operated there also.

Despite these doubts, other UK units started programmes with a handful of patients in Newcastle, Edinburgh and Birmingham in 1964–1965, but there was much opposition. A further critical editorial opposed to the idea of expanding provision of long-term dialysis dwelt particularly on the problems of hepatitis [34], which again threatened provision for acute renal failure. This provoked furious rebuttals from all the half-dozen active units then involved in long-term dialysis [35]. In response to this debate, the Department of Health convened a committee under the chairmanship of (then Sir, later Lord) Max Rosenheim in 1965 to investigate, and this looked to a working party led by Hugh de Wardener to recommend action. As a result of their reports, the Ministry of Health, in the person of the Chief Medical Officer Sir George Godber, moved rapidly in 1966 to begin setting up the recommended network of regional units within 5 years, and within 3 years 32 were already in action [36]. These units were intended to provide end-stage renal failure treatment, both dialysis and transplantation, to treat the expected 'suitable' British population of those in renal failure, which then numbered a little over 55 million in total. It was estimated that about 1500 (30 pmp) of the 7000 patients (134 pmp) dying annually at that time of renal failure, according to the Registrar-General's statistics for 1962, would be 'suitable' for long-term treatment. 'Suitability' was judged following those criteria originally suggested in Seattle, the principal limitations being that those aged 15–50 years of age without systemic disease and with a stable home environment would benefit the most. Funding for the new and existing units was initially from a

central budget. Clearly built into these suggestions was the explicit idea that not all those in renal failure could benefit from treatment, or should receive it: a new (and to most an unwelcome) concept in medicine. From being covert and accidental, rationing—by whatever name it was called—had become overt.

After this relatively promising start, stagnation quickly set in. Several factors played a role in this arrest of the programme. First, hepatitis B emerged as a major medical risk in the late 1960s and early 1970s (see Chapter 16), not only within dialysis units but often throughout whole hospitals. The perception of dialysis as a treatment was clouded by these epidemics in the United Kingdom to an extent not seen elsewhere in Europe, for reasons that remain unclear. Second and much more important, in 1971 the budgets for those units already in action was devolved from central allocation to hard-pressed local health finance officers, who often had little comprehension of the complexities, cumulatively increasing load and costs of a dialysis programme. Hardly any further units were established in the United Kingdom for 20 years. Even worse, in contrast to the funding system adopted in almost every other country, dialysis in the United Kingdom was funded not on the basis of a fee per dialysis, but on a workload-insensitive prior allocation of a fixed budget, usually renegotiated only on an annual basis.

The British health care system, in stark contrast to that in the United States, was a low cost programme (then 4–5% of a much smaller per caput GDP, today only a little over 7%) and was highly efficient, with overheads calculated to be 5% or less of expenditure. Its basis was the general family practitioner, each of whom had a 'list' of patients for whom he or she was responsible in sickness, and increasingly responsible also for promoting and preserving health. Access to specialist hospital opinion and treatment was obtainable only through this general family practitioner, who acted as what came later to be called the 'gatekeeper' of the service.

It has been widely stated that treatment for end-stage renal failure was initially, and still is, officially 'rationed' in the United Kingdom. This was and remains a myth, whose propagation—particularly in the United States—has suited the political ends of those promoting privately funded medicine through 'exposure' of the supposed evils of so-called 'socialized' medicine. The undoubted rationing was intrinsic to the British system, but the whole truth is much more complex and interesting [37,38]. First, it must be noted that the comparison of raw figures for numbers in renal failure between any countries is clouded by the differences in the incidence and prevalence of renal failure. Even before the availability of dialysis or transplantation, autopsy and death certificate data from the early 1960s showed that deaths from renal failure were almost twice as common in the United States (264 pmp/year) as in the United Kingdom (137 pmp/year). The major impact of both changing ethnicity in Britian and increasing age on the incidence and prevalence of ESRD has only had an impact—and been appreciated—in the past 15 years or so. Thus, raw intake figures cannot be used to compare how much need is being met. This is illustrated by the fact that some Scandinavian countries, which have had virtually open access to dialysis since the beginning, in addition to well-developed transplantation programmes, have take-on rates lower than many others in Europe—lower today in some Scandinavian countries than in the United Kingdom, and in all far below the figures from the United States [32].

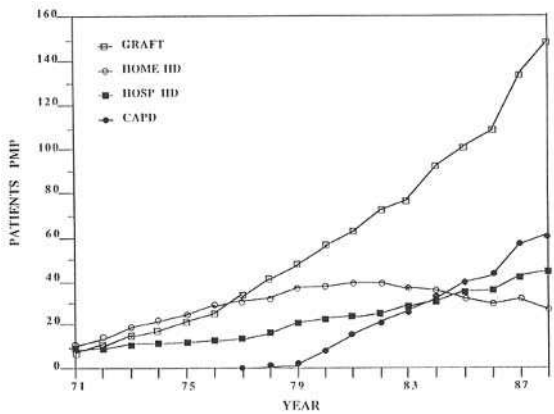

Fig. 21.2 Evolution of the proportion of treatments for end-stage renal failure in the United Kingdom during the 1970s and 1980s, from EDTA annual reports. A unique pattern emerged of heavy reliance on transplantation and home dialysis (HD) treatments (see text). (From [39].)

Nevertheless, the availablity of excellent data from the European Dialysis and Transplant Association (EDTA) registry from 1964 to 1991 allowed some comparisons to be made between European countries, and in the 1970s treatment rates in the United Kingdom began to lag behind those of most other large European countries (Figs 21.2 and 21.3). A large gap developed in the 1980s, especially in the treatment of older patients (at that time, defined as over 60 years of age) (Fig. 21.3). A unique pattern of care for patients in end-stage renal failure developed in the United Kingdom [39], relying heavily on the most cost-effective treatments of transplantation, or peritoneal and haemodialysis done in the home. Only now after decades of negotiation and protest has something even approaching full treatment of renal failure been achieved using a balanced provision of different types of treatment, including in-centre or satellite haemodialysis in quantity. But even today, patients over 70–75 years of age are still often not referred for consideration in the British medical system.

This pinpoints the major weakness of the arrangements for care in the United Kingdom. One feature of the years from 1966 onwards was that, in general, those running dialysis units in Britain were often not overwhelmed by patients, and rarely turned them down. Yet statistics suggest clearly there was evidence of a large unmet need, with take-on rates rising gradually and continuously from only 18 to over 100 patients pmp annually over 25 years from 1975 for the base population [40].

A pattern of behaviour emerged very early after the introduction of long-term dialysis: low expectations on the part of the population in general with regard to such 'exotic' treatments as dialysis; and a trust (often misplaced) in the opinion of the general practitioner or the local general physician that many patients dying of uraemia were 'not suitable for treatment', and therefore were not referred to specialist centres for an opinion [40]. There never was an official age limit for treatment by dialysis in British dialysis units, and in many units (including our own) anyone

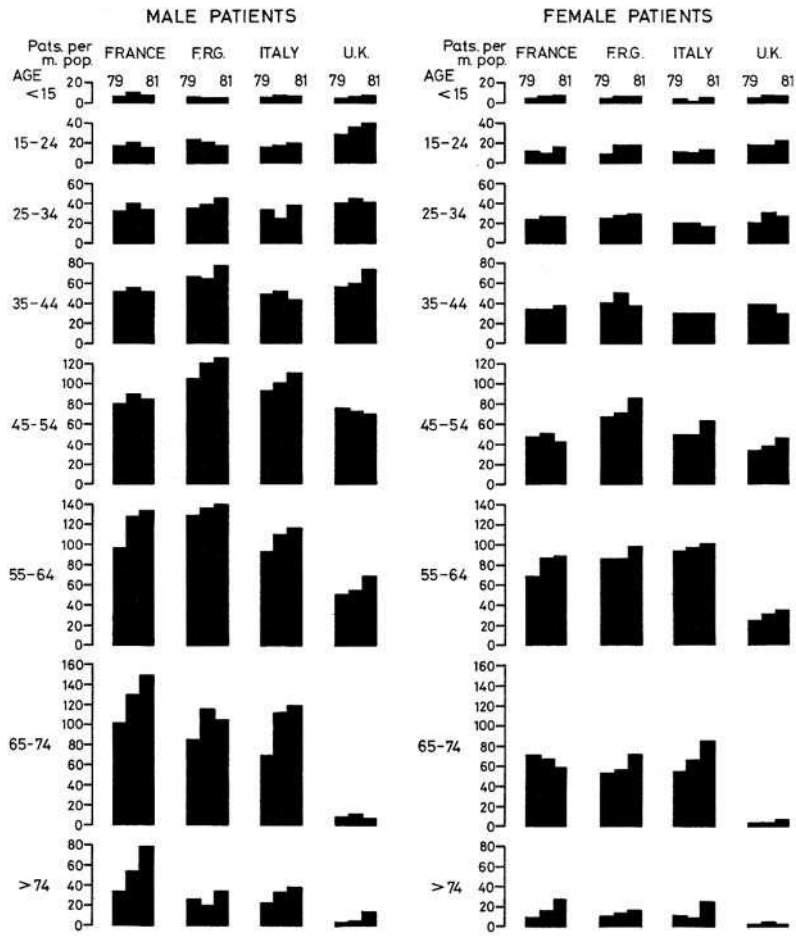

Fig. 21.3 Acceptance rates on to dialysis in selected European countries 1979–1981, demonstrating that the shortfall in treatment of renal failure in the United Kingdom largely fell on the elderly. (Data from the EDTA-ERA registry, courtesy Dr A.J. Wing.)

referred was treated, irrespective of age, right from the beginning; but *in practice*, for many years patients older than about 60 were rarely referred for treatment. Also, not all British dialysis units were so eclectic: in 1978 a British nephrologist could write in an article entitled with unconscious irony 'Standard British dialysis' [41]:

> fairly rigid selection criteria have been applied … all have been considered capable of managing self-supervised home dialysis. All were under 60 years of age … none had diabetes mellitus or amyloidosis as a cause of their renal failure.

In 1981 a controversial report was published from the prestigious Royal College of Physicians Medical Services Study Group [42]; in this an even longer list of criteria was cited as to why some patients—all under the age of 50—should be regarded as

'unsuitable' for dialysis, including 'poor command of English, parental irresponsibility, blind, orphan' and even (in 1981!) 'insulin-dependent diabetes'. This report was justifiably and strongly criticized as asking the wrong questions, and producing the wrong answers even to those. The origins of the dilemma are easy to find. As just noted, British renal units have had to run dialysis programmes within overall prenegotiated budgets, trying to maximize the numbers of dialyses performed and patients treated within these limits, rather than receiving an agreed reimbursement for each dialysis performed. The immediate providers of health care had to make impossible decisions, and as Caplan [43] of the Hastings Institute pointed out,

> [this] is a paradigmatic example of how physicians adapt when faced with the need to make tragic choices … the definition of medical suitability is redrawn to make the exclusion of certain individuals less painful for the decision makers … if the burden of allocation is placed solely on the providers … they will be in the position of having to justify by medical criteria what is basically a moral decision.

This lack of resources distorted also the balance between treatment modalities, overemphasizing the role of cheaper treatments such as home haemodialysis and (from 1980 onwards) home CAPD (continuous ambulatory peritoneal dialysis) against the most expensive option of in-centre haemodialysis. The number of in-centre dialysis places still remains well below requirements in the United Kingdom, and patients have never yet enjoyed a free choice of treatment modality.

These various strategies of occult rationing (usually referred to euphemistically as 'prioritization') suited successive governments of different political flavours and Department of Health professionals, since they were directly responsible for all the costs of dialysis from the beginning. In addition, dialysis provision suffered even more than established services from the repeated reorganizations of the NHS from 1974 onwards, with confusion about where in the system real fiscal responsibility rested, and decisions about expensive treatments such as renal failure should be made. The failure of primary referral resulted in physicians, patients and their organizations and relatives not having a 'body count' to convince politicians and health administrators of the short fall.

Gradually, however, lobbying had some impact; in 1978 the Office of Health Economics produced a review of renal failure in the United Kingdom which highlighted the shortfalls [44], and numerous editorials and articles appeared in the popular and medical press [45]. In 1984 the government, represented by then Minister of Health John Patten, recognized a national target intake of 40 patients pmp/year on to dialysis treatment to be achieved by 1987—but without specifying where the local health authorities were to find the funds to achieve this; many simply did not provide them [46]. Nevertheless intake and prevalence rates for dialysis slowly climbed (from 20 pmp in 1980 to 67 pmp/year in 1992) and in that year the Renal Association of the UK produced a new estimate that a minimum intake of 80 pmp/year was necessary, based on new surveys of the prevalence of renal failure in England and Northern Ireland which they helped sponsor. In 1990 Tony Wing summarized the impact of these studies and the position of dialysis in the United Kingdom succinctly [47], as yet another reorganization of the NHS was engineered. This 80 pmp/year figure was accepted by the government's Renal Review of England conducted in 1993–1994, and became the target for the 1990s. In 1998, almost everywhere throughout England

90 pmp/year had been approached or exceeded, and in Scotland, Wales and Northern Ireland, despite very small ethnic minority populations with their higher rate of renal failure, figures of 105–128 pmp/year were achieved giving an overall intake for the United Kingdom of 96 pmp/year for that year [48]. What the ultimate intake will be remains to be seen—probably a figure of about 130–140 pmp/year, remarkably close to the Registrar General's estimate from 1962. In parallel, the number of units has slowly risen during the 1990s to a current total of 73—still a ridiculously small number for a population of now 59 million—although this does not include a count of the many satellite units which are run from the base unit, again a development mainly of the 1990s. The average number of patients with ESRD looked after by a single unit in the UK is 400–500, and a number care for twice as many patients as this.

Thus it has taken more than 25 years of effort, lobbying and education by patient groups and involved professionals before the United Kingdom services for renal failure even approached being able to treat most of those who 'could benefit' from intervention. But this last sentence contains the central dilemma of the application of haemodialysis treatment today—a subject which requires its own essay. The improvement has almost entirely been in reaction to agitation and pressure from below at the customer level, helped along by only some members of the medical profession, rather than by intelligent planning from above. It is difficult not to remain angry at the suffering and neglect of British patients with renal failure over the decades of the development of treatments for renal failure, at root the result of a tacit choice by governments of all types to continue spending (however efficiently) a much lower proportion of national wealth on health care than that thought appropriate throughout the remainder of the industrialized world (see Chapter 22).

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An important forecast of numbers of patients requiring treatment in the United States up to 2010, again using Markov analysis, was published recently (Xue JL, Ma JZ, Louis TA, Collins AJ. Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. J Am Soc Nephrol 2001; 12: 2753–2758). This study predicts an incidence of 129 000 p.a. and a total prevalence (including 179 000 with transplants) of 700,000 in that year, costing $28 billion p.a., (unadjusted for inflation). However, this analysis was based on data to the end of 1998, and the fall-off in the rates of increase and increased death rate in 1999 was not taken into account. These figures therefore may represent a maximum rather than a likely outcome; but of course equally the 1999 data may be seen as an aberration when the data for 2000 emerge this year.

Chapter 22

Conclusions: dialysis today—and tomorrow?

Haemodialysis represents the successful application of physical chemistry and physiology, together with materials and mechanical science to a pressing clinical problem which it neither prevents or cures, but only palliates. As such, it represents an archetypal 'halfway' technology [1] and involves major ethical, social, political and financial problems: in many ways it is a paradigm of the problems facing much of twenty-first-century medicine in developed countries. A number of the pioneer clinicians whose work is reviewed in earlier chapteres are still present to see the consequences of their work, and continue to contribute eloquently to the debate on these dilemmas.

Basic dialysis technology: more of the same

Since the broad pattern of haemodialysis became settled around 1970 much has happened; but as emphasized from the outset of this account, the basic technology and the broad agenda of haemodialysis have remained the same during the past three decades. Attempts to make radical changes to the usual procedure of haemodialysis, such as the addition of absorption, have failed so far. It comes as a surprise and a disappointment to find that almost no progress—apart from the use of single needles—has come in access to the circulation for dialysis: many attempts to provide direct needle-free access to blood vessels have failed. We argue still about how to quantitate dialysis, and debate the nature of uraemic toxicity in ignorance as profound as that of the 1960s or even the 1900s! This is a crucial gap, because without a better understanding of what we are trying to achieve, progress will always be slow, limited and empirical using surrogate markers for what is important by its absence in renal failure.

We argue still about when it is best to begin dialysis: in the 1960s, shortage of dialysis places predicated the latest start possible, often after a period on ultra-low protein diets and sometimes coincident with them, as in Scribner's initial experiments. Now, the question of whether 'early start' dialysis to supplement and maintain renal function rather than waiting until late uraemia is preferable, as Bonomini suggested in the early 1970s, has become a moot point. Machines have become much more user-friendly; new more biocompatible membranes, far smaller dialysers and more sophisticated programming and controls have eliminated the 'home-made' look and feel of the 1960s dialysis unit. Dialysis is also, thanks to sequential or

programmed ultrafiltration and the use of bicarbonate rather than acetate dialysis, a much more pleasant experience for the average patient; although the bicarbonate has raised again problems of bacterial growth and absorption of bacterial products into the blood stream, even through intact membranes, and has started a debate about the use of ultra-pure water for dialysis. Dialysis times shortened during the 1970s and 1980s, but now are lengthening again partly in response to the dip in survival rates recorded during the 1980s. Haemodialysis at home has become the choice for only a minority of patients today, but satellite and minimal care units have boomed. An old idea, daily haemodialysis in the home, pioneered in the 1970s, has made a come-back in the 1990s with simpler dialysis machines and procedures. However, the actual process of dialysis remains essentially similar, only the shift towards convective treatments using highly permeable membranes having had a major impact on the basic technology.

Of the 'old-fashioned' complications of uraemia discussed in Chapter 16, cardiovascular disease still presents a growing and daunting challenge [2], but bone disease is now controllable in most patients using a modern version of vitamin D and calcium control. However, the need for the primitive act of chopping out dysfunctioning endocrine glands from the neck is, amazingly, still with us occasionally for patients in the third millennium—one can hope for not much longer as new forms of vitamin D and calcimimetic agents are developed. Since 1987 epoetin has permitted the dialysis patient to enjoy a vastly improved life through the control of anaemia, although we still argue about whether or not to correct this completely, a ghost discussion from past decades based on debate about costs with no real foundation in science or medicine. Together with the introduction of the arteriovenous fistula, the introduction of epoetin has probably been the single most important advance in dialysis patient care in the past half century.

Transplantation at last provides a safe outlet for a number of (mostly younger) patients, which is fortunate as haemodialysis for longer than 10 years or so is still associated with a crippling prevalence of β_2-microglobulin amyloidosis, a complication of uraemic toxicity unknown and unpredicted in 1970. Perhaps more biocompatible dialysis will help, although more probably absorbents will be the answer: time will tell. Amyloidosis has not been the only 'new' plague for the dialysis patient: other blood-borne viruses such as hepatitis C are now recognized to be more dangerous than hepatitis B, and the unforseen pandemic of AIDS beginning in the early 1980s has touched dialysis, as it has every branch of medicine, but especially because of the dependence on blood access for dialysis treatment.

Despite the many problems of long-term dialysis, and a failure to normalize expected survival rates for patients of any age, even the young, potential survival on haemodialysis has been remarkable. The achievement of Professor Robin Eady and his carers has been mentioned and illustrated in Chapter 14; he spent 25 years on continuous haemodialysis, 23 years of this as self-dialysis at home, before being successfully transplanted 14 years ago. Jean Tarver, a patient in Oxford, England began peritoneal dialysis on Christmas Eve 1966, transferred to haemodialysis in August 1967, and died aged 74 in November 2001 just short of 35 years of dialysis treatment, surviving amyloidosis during the 1980s, a minor stroke, and breast cancer. She

worked and raised a family as well as dialysing herself at home from 1968 to 1984, and is the longest surviving patient of whom I have details. Recently the death of a patient in Liverpool, England who had survived for just over 30 years on uninterrupted home haemodialysis was reported [3], although he was crippled by dialysis amyloidosis and suffered severe vascular disease, from which he died. More fortunate were two German patients started on home dialysis by Shaldon in January 1970; one died in 2001, also from long-standing coronary arterial disease for which he had bypass surgery, but the other continues on dialysis at the time of writing, approaching 32 years later, without interruption. Born in 1938, this patient has been using the same arteriovenous fistula all this time, and remains in good health.

In Italy, a female patient of Vincenzo Cambi's in Parma started peritoneal dialysis for one year in 1967 aged 27, but has remained on continuous haemodialysis ever since, now approaching 34 years in duration. She has heavy calcification of her arterial tree, which led to surgery for ischaemic bowel symptoms, and has required bilateral operations for carpal tunnel syndrome but is otherwise well. An additional patient in Piemonte has been on haemodialysis for more than 30 years. I have not been able to obtain, as yet, any details of a remarkable Japanese patient reported as having been on continuous dialysis for more that 35 years, nor sadly have I identified any patient in the United States who has survived more than 25 years on dialysis.

Dialysis: social and financial context and the 'dialysis industry'

In contrast to the continued similarity of basic dialysis procedures, the social and financial context within which dialysis is performed has changed radically since the 1960s. Early acute dialysis was entirely within hospital departments of medicine and surgery, often in the setting of a university hospital, in which the development of new technology took place. Baxter Laboratories in the 1950s developed commercial products to meet the need for haemodialysis and peritoneal dialysis reactively, but only in response to approaches by inventive and innovative clinicians—in these instances Willem Kolff and Mort Maxwell. After the introduction of long-term dialysis, during the 1960s the initiative for development gradually moved to industry, and was complete by 1970 [4,5]. Since then few technical developments have taken place within dialysis units themselves—the outstanding exception being the development of continuous ambulatory peritoneal dialysis (CAPD) and other equilibrium techniques of peritoneal dialysis during the late 1970s and early 1980s. Usually the relationship has been that the clinicians have identified a clinical need, and industry-based research has tried to find the answer to that need. On occasion industry has evolved new technology and then tried to persuade clinicians of the benefits, real or imaginary, of this new technology. Often this has not proved successful, and suggests that the relationship should be that the problems requiring solution should be identified within the experience of the dialysis unit and its patients, and not at a corporate level.

But this ignores the salient fact that today the majority of patients in the developed world are dialysed in or by units run directly or remotely by major corporations, progressively fewer in number as mergers take place, and frequently owned and run outside the country in which they are operating, the majority being based in the United

States. In most cases these corporations are also manufacturers of products which are used within the dialysis units they run. The cycle of product and procedural improvement in dialysis treatment is now largely within a continuous circle of commercial development. Meanwhile, almost everywhere government, directly or indirectly, foots the increasing bills (see below).

Dialysis is a treatment, and to reach patients in need of it it must be delivered through a system of *health care delivery*. As Lameire and his colleagues [6] remind us:

> health care systems … are strongly influenced by the underlying norms and values prevailing in the respective societies … [they] often reflect deeply rooted social and cultural expectations of the citizenry. Although these fundamental values are generated outside the formal structure of the healthcare system, they often define its overall character and capacity … [they] are strongly influenced by each nation's unique history, traditions and political system. In some societies health care is viewed as a predominantly social or collective good, from which all citizens should benefit … other societies, more influenced by the market-oriented thinking of the 1980s, increasingly perceive health care as a commodity that should be bought and sold in the open market.

All systems in Europe have their basis in the first view of health care, whilst in the United States the latter view strongly prevails. Three different systems of health care can be identified [7], within which dialysis, like all health output, is purchased and delivered (Fig. 22.1). These are the two poles outlined in the quotation, on the one hand the 'Beveridge' model based on taxation, and on the other the private insurance model as found almost exclusively in the United States. In addition there is the 'Bismark' mixed model, financed by a premium social insurance system and used not only by central European countries but also in Japan.

Within each and all of these models, the actual care can be provided by public agencies, by private health care corporations, or by a mixture of both. Not surprisingly the proportion of public and private provision varies from country to country, although all those countries adopting the 'Beveridge' model of centrally funded care in Europe have so far opted for exclusive or predominant public provision, with the exception of Spain where, uniquely, the proportion is about half private and half public. In

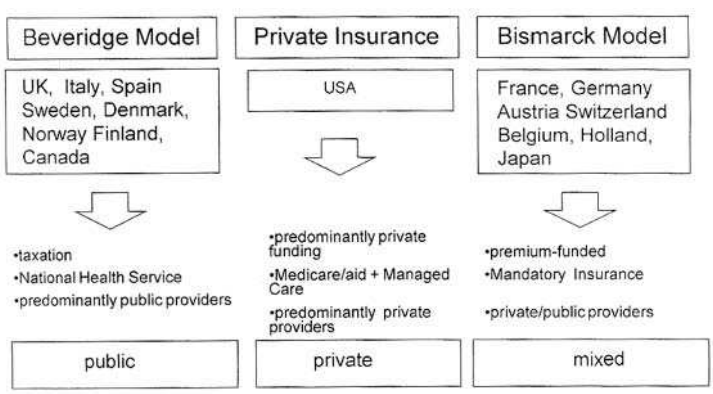


Fig. 22.1 Health care systems in the industrialized world (see text for discussion). (From [6] with permission.)

contrast the provision of dialysis in the United States is now overwhelmingly through private corporations (77% in 1998), although some of these units are wholly owned and run by universities and hospitals. This 'privatization' of dialysis in the United States during the 1970s generated a vigorous debate during the 1980s (described in Chapter 21) as the programme expanded and costs exploded. The amounts of money then spent, although seemingly modest by current standards, raised intense debate as to whether for-profit dialysis gave equal or better value than dialysis in non-profit-making hospital or university facilities, or that industry was creaming off large profits from the taxpayer's pocket.

Locked into this debate were arguments as to the applicability and costs of home dialysis compared with free-standing or hospital unit dialysis (see Chapter 21). There is no doubt that the potential role of home haemodialysis was exaggerated in both the United States and the United Kingdom during the early years of the 1960s and during the 1970s by the enthusiasm of the pioneers of long-term dialysis, reinforced by the cost advantages to the final purchaser—the state. This may have been appropriate for the carefully selected patients (see Chapters 16 and 21) of that era, but most of the widening range of patients entering treatment in the 1980s and since neither

Table 22.1 Numbers of patients on dialysis in Europe

	Haemodialysis		Peritoneal dialysis		
	Home	Centre	Intermittent	CCPD/ CCPD, etc.	Total
1965	168		?	–	168
1966	296		7	–	303
1967	621		?	–	621
1968	1281		?	–	1 281
1970	3100		50	–	3 150
1975	4305	18 116	336	–	22 757
1980	7838	40 507	910	1839	51 157
1985	7441	67 328	985	7529	83 283
1991	4568	97 447	1117	14 057	117 189
1995*	2498	136 330		21 297	160 125
2000					? 180 000†

CAPD/CCPD, continuous ambulatory/cycling peritoneal dialysis.

* The 1995 estimates are based on data from 15 EU countries with a total population of approximately 375 million (data from: Jacobs C.J *Nephrol* 2000; 1 2 (Suppl 2): S47–52).

† No comprehensive data for the whole of Europe are available since 1991. In this context, 'Europe' represented 35 countries in Europe and around the Mediterranean littoral. The EDTA registry has re-formed as an association of European national registries: to begin with only six countries reported full data to it (see: van Dijk PCW *et al*. *Nephrol Dial Transplant* 2001; 1 6: 1120–9). National registries are available in a number of other European countries, however (see the year 2000 USRDS report: *International comparisons*). From these data one can derive that for the EU countries plus Czechoslovakia (population 18 million) and Poland (population 36 million), the prevalent ESRD population in 1998 was approximately 245 000, of which more than 180 000 were receiving dialysis, whilst the remainder bore renal transplants.

wanted—nor were capable of—home dialysis. Ironically, the absolute number of patients doing home haemodialysis actually increased until the early 1980s, even though the proportion on this type of treatment fell away (see Tables 21.1, 22.1 and Fig. 21.3), although it remains relatively popular in Britain, Australia and New Zealand. This trend away from home haemodialysis was accelerated by the introduction of CAPD in 1978–1980, which provided a home-based method of treatment with many advantages over haemodialysis, especially if dialysis for only a few years was expected (see Fig. 19.4).

Today the vigorous debate outlined in Chapter 21 continues on commercialism of dialysis centres, but on an international scale. In many counties such as Argentina and Portugal only a handful of for-profit providers account for almost all haemodialysis. The debate centres mainly about who is dialysed or should be dialysed; whether there is adequate choice of treatment modality and schedule; whether there is equal access to transplantation; and finally whether adequate amounts of dialysis are prescribed and actually delivered. This last topic has been the subject of the greatest debate, initially using flawed and non-comparable statistics, but which eventually did show consistently that American survival data of the 1980s had become worse than even carefully matched outcome data from Europe and Japan. An examination of the amounts of dialysis prescribed and delivered was handicapped by a lack of agreement on, and intrinsic flaws in, the analysis of dialysis adequacy as discussed in Chapter 17.

It has been clear almost from the beginnings of dialysis that choices of end-stage renal failure treatment, both in terms of type of therapy or its detailed delivery now depend largely, not on purely medical input and patient preference, but upon non-medical factors. These arise either as a result of government legislation, fiscal allocation or even inaction, or upon commercial and fiscal pressures and other constraints operating within the state, but particularly the private sector. The central issue involved is how many patients are treated in the first place, which depends in turn in most countries upon financial resources made available for health care by government (Fig. 22.2). The behaviour of the UK and US governments in this respect was analysed in detail in Chapter 21. Secondary issues concerning choice arise also: for example the proportion of patients receiving peritoneal dialysis or home haemodialysis and the proportion bearing a functioning transplant are consistently higher in

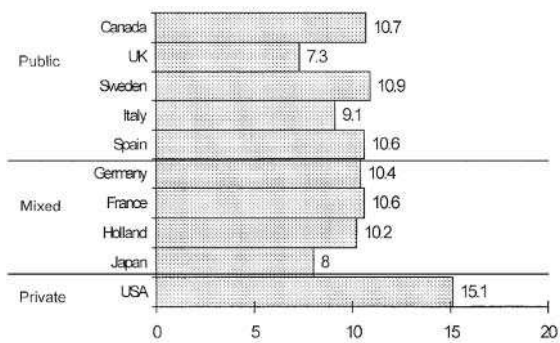
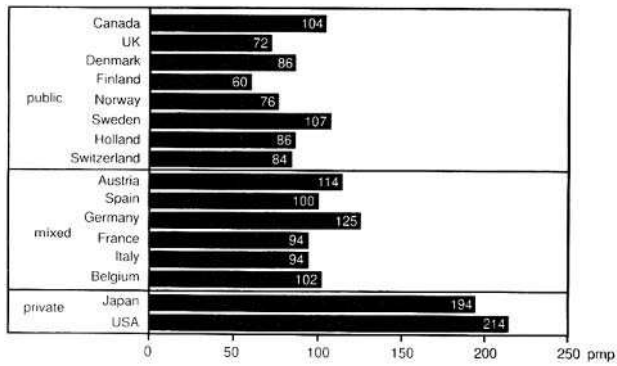
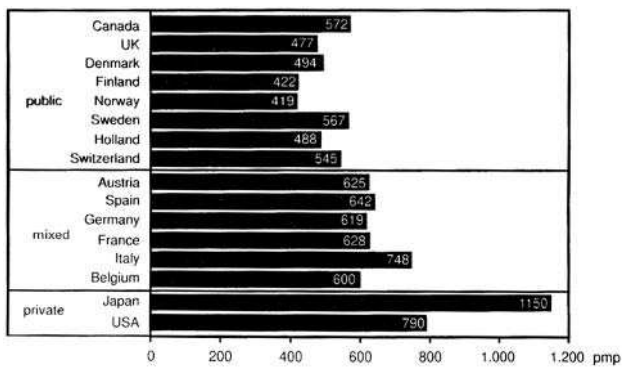


Fig. 22.2 Estimated expenditure on health care in 2000 as a percentage of the gross domestic product in industrialized nations. (From [6] with permission.)



(a)



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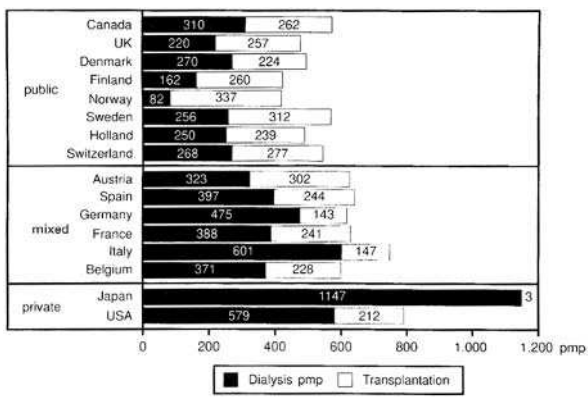
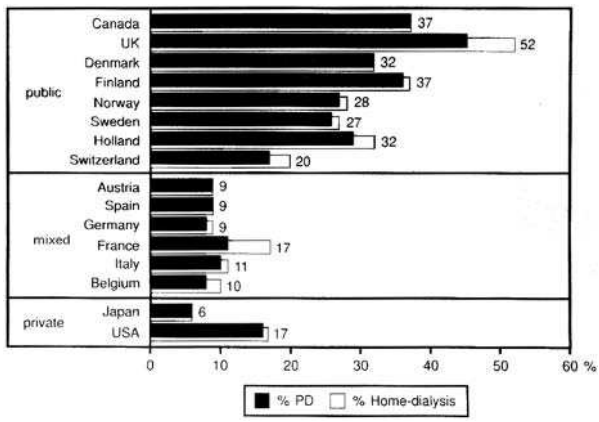


(c)

Fig. 22.3 The relation between health care systems and the level and type of treatment of end-stage renal failure in industrialized nations in 1994–1995. (a) Intake per million population (pmp) per year; (b) total prevalent patients pmp; (c) prevalent patients pmp on dialysis and with a functioning transplant;



(d)

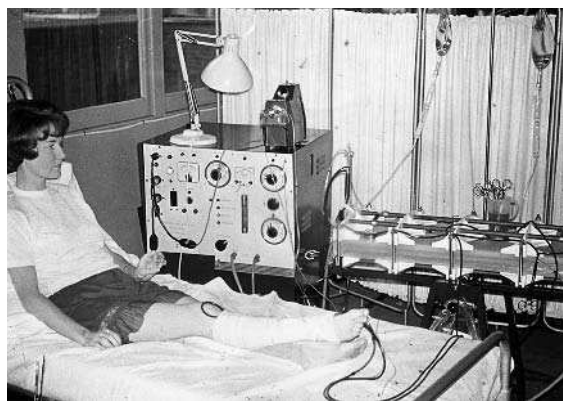
Fig. 22.3 (d) proportion of patients on dialysis receiving home haemodialysis and peritoneal dialysis. (From [7] with permission.)

publicly provided systems when compared to 'mixed' (Bismark) type systems using private delivery of dialysis or to the United States' model of private insurance (Fig. 22.3) [6–10]. For example, internationally the use of CAPD varies between countries from a negligible 4% of those on dialysis in Japan (Table 22.2) to more than 90% in Mexico (see Fig. 19.3). At a more individual level, how long a patient dialyses at each session is likely to be determined by local issues of costs, of staffing and scheduling as much as by perceived medical need, whatever system operates. For example in the United Kingdom, even in 2001, a few local health authorities still will not fund thrice-weekly dialysis or erythropoietin for all who need it.

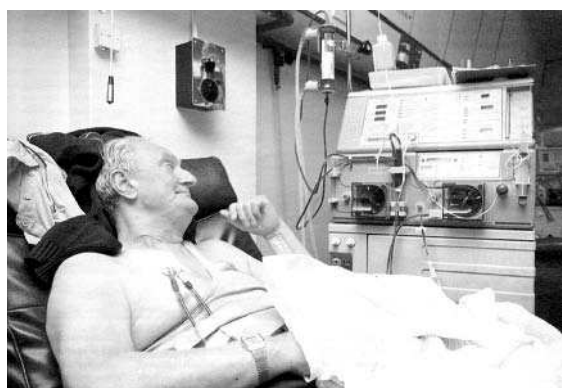
Finally, the debate on selection of patients has not gone away, even in the industrialized world, as recent papers from the United States [11], Canada [12] and inevitably the United Kingdom [13] show. The issue of withholding dialysis appropriately has been discussed in Chapter 20, and morally should be within a framework of striving to achieve the best and most appropriate care for the individual patient. However, health economists and government paymasters must also have an interest in limiting expensive treatments to a population of those who can 'benefit' from it, judged in health economic terms and justified by the lost opportunity costs of money spent on 'futile' treatments, which could more usefully be spent elsewhere within the health budget. In no country, however rich, is the public purse bottomless, and thus there is an essential and necessary tension which cannot be resolved without a debate, which attempts to assess simultaneously the relative value of diverse treatments to society as whole, and to individual patients. There is no escape from this debate, however much is spent on health care, but adequate resources can shift the arena of debate into easier territory. A major problem in this area is that the tools so far available for economic comparisons of quantitative (and especially qualitative) treatment outcomes are clumsy and inaccurate, even though often adopted eagerly by naïve—or manipulative—administrators.

Dialysis patients then and now

If one can argue that basically haemodialysis has remained the same in all but important detail, in contrast the patients under dialysis treatment are now radically different (Fig. 22.4). First in their number: from only about 5000 in the whole world under treatment for end-stage renal failure in 1970, mostly aged from 20 to 40, approaching one million are now maintained on dialysis (see Tables 21.1, 22.1 and 22.2); in both



(a)



(b)

Fig. 22.4 (a) Haemodialysis in the 1960s: the patient is young; an external Teflon–silastic arteriovenous shunt in the leg is being used without a blood pump; the monitor is crude with few functions; the flat-plate dialyser is rebuilt every two or three dialyses, and is huge and poorly efficient; and dialysis is long and usually done in the patient's own home, often overnight. (b) Haemodialysis in the 1990s: the patient is elderly; a subclavian jugular line is being used for access with a blood pump; the monitor is streamlined and compact with many functions; the hollow-fibre dialyser (top centre, vertical) is disposable, tiny and highly efficient; and dialysis is being done in a highly professional unit.

Table 22.2 Number of patients on dialysis in Japan*

Year end	Total	Home dialysis (%)	Peritoneal dialysis	
			CAPD/CCPD (%)	IPD (%)
1970	ca. 500		–	
1975	13 250		–	
1980	36 397		0	
1983	53 017		0	
1985	66 320		0.5	0.1
1990	103 296		2.6	0.1
1992	123 926	0.1†	4.9	0.1‡
1995	128 102			
2000	206 134§	NA	4.3¶	

CAPD/CCPD, continuous ambulatory/cycling peritoneal dialysis; IPD, intermittent or other forms of peritoneal dialysis.

Source: Japanese dialysis registry reports.

* The overwhelming proportion of end-stage renal disease (ESRD) patients in Japan are treated by in-centre dialysis. In 200, 78.4% of all patients were on haemodialysis treatment in privately run clinics, and 21.6% in public and semipublic units.

† 111 patients.

‡ 106 patients.

§ Includes about 5000 Japanese patients who bore transplants in 2000 – the exact number unfortunately is not available.

¶ 8856 patients—the absolute number of patients on CAPD in Japan is still rising, although the proportion remains approximately constant.

the United States and in Japan today, *more than one in every 1000 individuals is receiving dialysis treatment for end-stage renal failure*. In Italy the corresponding figure is one in 1100, and in all industrialized countries it is more than 1 : 1500.

The second major change has been the rising tide of diabetes, which is described in detail in Chapter 20. Today the single commonest cause of renal failure is diabetes in every country and community. The third major change has been the 'greying' of the dialysis population. This has in part followed the greying of the general population—in 1960 in industrialized countries about 8% of the population was aged over 65 years; in 1994 the proportion averaged 14.5% [6], is still rising and is predicted to reach 26% by 2030. The increase in those aged 80 or more is even more striking, it is now 3% but is predicted to triple to over 8% by 2030. In addition it is well-known that end-stage renal disease has been revealed as predominantly a condition arising in the elderly. As a result of these two pressures, more than half of patients on dialysis today are pensioners over the age of 65, many of whom suffer an increasing burden of other age-associated diseases. Patients in their eighties are common, in their nineties unremarkable, and even a few centenarians are under treatment. In the European

Union, Japan and North America, *the size of the prevalent cohort of 80–90 year olds under dialysis treatment now exceeds that of the 20–30 year olds*, and long-term dialysis has all but become a branch of geriatrics. As Fernando Valderrábano has remarked [15], to have discussions and published papers on 'dialysis in the elderly' is a nonsense: dialysis *is* in the elderly, and we should, perhaps, be talking more about the 'special problems' and 'unusual needs' (for example paid employment) of the minority of young adults on long-term dialysis!

Whether or not *all* elderly patients in renal failure, however handicapped or compromised, should be treated has been much debated. In practice, even in the United States some tacit rationing is applied [16] and dialysis is not alone in this: the elderly do not receive equal treatment as their younger peers in any form of life-saving therapy, anywhere in the world [17]. Thus the need for dialysis is likely to rise even more sharply than predicted from current figures.

A further crucial point it is easy to forget in the glossy high-tech dialysis units of North America and Europe is that its high cost means that, for the majority of patients with renal failure in the huge, teeming poorer countries of the world, dialysis is not an option except for the rich or the privileged [18]. This is despite the fact that renal failure is five or 10 times as common as in the developed world—a throwback to their history, as we discussed in Chapter 1 [19]. For example in India, a country now comprising more than one billion individuals, *it is certain that several hundred thousand people go into renal failure each and every year*, the vast majority of whom receive no treatment whatsoever except for a lucky few who are mostly transplanted from living donors. Figures for China are unknown but are probably similar, except for the origin of the kidneys transplanted in that country. The more urgent need, however, for these populations is not for dialysis or even transplantation, but decent social conditions to live in so that renal failure can be largely prevented, as it has been already in the industrialized West [19].

Has dialysis a future?

It may seem superfluous to ask this question, when the numbers of patients treated by dialysis are still climbing, albeit at a slower rate than in previous decades. However, we can never forget that dialysis is only the postponement of a problem, and not a solution. It tides the patient over, but for what? Where will dialysis be in 10, 20 or 30 years ahead?

For those going into *acute potentially reversible renal failure*, whose prevention remains elusive and whose mortality remains obstinately high, some form of diffusive or convective treatment seems to be necessary. I have argued throughout this book that acute renal failure is largely the result of partial success in the treatment of severe acute illness, survival from increasingly compromising metabolic assaults permitting the later development of acute tubular necrosis. Therefore I cannot see prevention ever being able to eliminate acute renal failure, even if a comprehensive renoprotective strategy can be evolved, for the simple reason that some events leading to acute renal failure occur at random and cannot be pre-empted; earthquakes and the crush injuries they lead to are an example of this, and the recent Turkish disaster

of 1999 showed that despite prompt and effective prophylactic treatment, many cases of established acute renal failure arose which were treated, however, with an amazingly low mortality [20]—largely by conventional intermittent haemodialysis, it might be added. Despite the lack of convincing evidence of improved survival over more traditional methods of dialysis, some form of continuous convective and/or diffusive treatment, applied prophylactically if necessary, seems instinctively the best way to go since it mimics normal physiology most closely.

As for *chronic irreversible renal failure*, in 1992 I was foolish enough to predict in public [21] that by 2005 dialysis would be necessarily present only as a temporary adjunct to successful xenotransplantation. As so often happens with predictions, this has foundered on facts unrecognized, but even so predictable at that time.

Dialysis for chronic renal failure developed coincidentally at about the same time as successful *clinical transplantation*, and throughout the period there has been a fruitful interaction between these two fields of enquiry. Although successful transplants between identical twins were achieved during the mid 1950s, transplantation was quantitatively insignificant as a treatment for chronic renal failure during the 1960s, although it held out much hope for the future. A number of transplant programmes were begun in many countries in the early 1960s using both living and cadaver donors, but were abandoned by 1966 in the face of appallingly poor results, only to be re-started later in the decade [22]. Even by the end of the 1960s, the mortality of the young recipients given cadaver transplants at that time remained high (25–40%), in retrospect largely the result of inappropriate immunosuppressive regimes, and even worse after only 5 years 80%of the transplanted kidneys had already failed. Even recipients of living donor kidneys suffered substantial mortality. Only a handful of patients were alive with a functioning graft in 1965, and even in 1970 no more than a few hundred at most. In the face of these dangers, during the 1960s many patients preferred the known risks of dialysis even to the chance of a much better life with a transplanted kidney.

Then during the 1970s and especially the 1980s, transplantation became clearly the better option for treating chronic renal failure in younger patients. Cautiously, with better understanding of immunosuppression and new agents such as the introduction of cyclosporine in 1978, it was extended to older and older recipients, so that by the end of the century the dangers of transplantation in selected 70–80 year olds now seem to be no greater than those of dialysis. Nevertheless, for a large group of more frail elderly patients with renal failure and associated diseases, dialysis still seem to present the best option.

Is dialysis, then, about to retreat to the margins of the very young and the very old, or as a preparation for dialysis? Unfortunately not. Even in the young, transplantation is still severely handicapped by two factors. The first of these is chronic loss of grafts. Although over the past 25 years, the proportion of cadaver grafts surviving the first year has risen to over 90%, beyond this point the functioning half-life of the organ persists at only about 7.5 years, without any improvement whatsoever. The other, even more important (since retransplantation is possible) is the continued shortage of donor organs. Even the best cadaver donor programmes in the world, such as the Spanish Organización Nacional de Transplantes (ONT), can generate only about 60

kidneys per million population (pmp) per year at present, even though potentially perhaps twice as many as this could be available. If (as in Norway) living donors are equally exploited as well, then using current criteria for those who may be suitable for transplantation, waiting lists can be maintained approximately constant at reasonable numbers or even reduced. But this is only true if large numbers of those in renal failure are deemed 'unsuitable' for transplantation, especially those aged over 65 or 70 years of age. Without access to xenografts, to transplant in excess of 100 pmp/year at present seems impossible.

The recent history of xenografting has been one of hopes raised then to be dashed [23]. Not only are the long-term immunological consequences of xenografting still unknown, now that the immediate natural antibody reaction seems to be avoidable, but the spectre of animal retroviruses which may 'highjack' the recipient's own genome [24] has all but halted applied research until this problem is sorted out. The difficulty may be that in the end the only way to know what may happen is to try a pig-to-human transplant, with the risk not only that the recipient may acquire unforseen diseases from the retroviruses, but that these might be transmissable to other human hosts, thus starting an epidemic.

Thus it seems likely that dialysis will be needed for many decades yet, as long as chronic renal failure arises. But what are the chances and the possible timescale of making major inroads into the numbers entering chronic renal failure by preventative strategies?

Here we must consider the residual 100–200 pmp/year going into renal failure who persist even after improvements in nutrition, hygiene and infection rates, i.e. the situation in the developed West [19]. Although even in industrialized societies there is a gradient of incidence with poverty, highest in the poorest of the community, there are no prospects for making major inroads into these figures any more in the West. At several points in this book I have pointed out the often forgotten fact that the incidence of chronic renal failure in the United States has always been very high, probably double that of countries such as the United Kingdom and Denmark for which comparable statistics exist from the immediate pre-dialysis era (264 vs 134 and 137 pmp/year, respectively). These data suggest that in most European countries treatment intake, given demographic changes in the past 50 years, will plateau at about 150 pmp/year, whereas in the United States more than 300 pmp/y can be expected and had already been reached in 1998. Indeed, the rate of increase in intake numbers is beginning to flatten off as such figures are approached or exceeded (ca. 120 and 309 pmp/year, respectively, for Europe and the United States in 1997 and 1998). Some time thereafter, the prevalent numbers on end-stage renal failure treatment will plateau, probably at or below about 1200 pmp in Europe; but already Japan and the United States have passed this figure and will need to sustain much higher numbers. Markov chain analysis (the main tool used for analysing future trends) shows how sensitive the final figures may be to quite small changes in estimates of outcome from individual treatment stages, and make any detailed estimate unreliable.

Palliative treatment by dialysis of the majority of these patients will continue, for the next decade or two at least, to consume major health resources. Despite large (fivefold) variations in total amount spent on health care, the proportion spent on

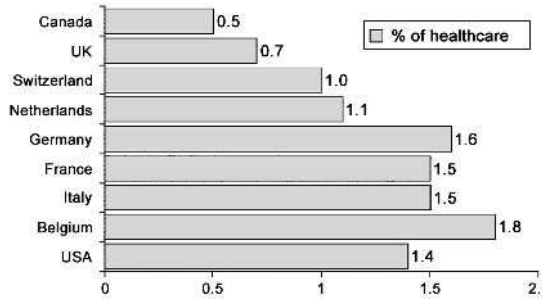


Fig. 22.5 The percentage of total heath care spend allocated to the treatment of end-stage renal disease in various countries in 1997. (From [10] with permission. See Permissions.)

renal failure services is much narrower—currently from 0.5% to 1.8% (Fig. 22.5) [8], with most countries around the 1.5% mark. This proportion of total health spend goes to treat the 0.03–0.06% of all patients who are treated for end-stage renal failure, emphasizing the low-volume, high individual patient cost nature of dialysis treatment.

Can we prevent renal failure?

Will we see a fall in the number of patients entering renal failure? What can prevention achieve? The principal cause of the 'residual' renal failure everywhere in the industrial world is now diabetes mellitus. We know both that tight control of hyperglycaemia over the years will diminish the numbers of diabetics entering renal failure in both type I and type II diabetes, and that the proportion of type I diabetics with renal failure halved during the second half of the twentieth century (see Chapter 20). However, with over 1% of industrialized Caucasian populations developing diabetes, and a much higher prevalence in populations of differing ethnicity, it may be that this will only serve to slow the rise and not reverse it at all. Only efforts to limit the development of diabetes itself, through diet and weight control, are likely to have a major impact and the difficulty of achieving this is obvious. Even so the recent success of relatively modest changes in lifestyle on the incidence of type II diabetes in Finnish men reported recently [25] suggests the effort is well worth making.

For many years the fact that treatment of hypertension would ameliorate renal failure has been evident, irrespective of the agents used. We know also that treatment with ACE inhibitors has a powerful renoprotective effect even in established diabetic nephropathy, and also in proteinuric non-diabetic disease. Just how much can be achieved using this type of strategy, alone or in combination with other agents such as AT1 receptor inhibitors, is not clear yet and is the subject of much contemporary debate. Certainly dialysis can be postponed for several years in this way, which in the numerous elderly patients with renal failure may mean altogether. Limitation of protein intake, as we have seen earlier in the book, has a long history in the treatment of renal failure. Despite difficulties of definition and application, low-protein diets again appear able to postpone dialysis for 6 months up to a year or two, although their potential is not as great as pharmacological manipulation. Finally, control of lipid

concentrations protects uraemic animals, although human data have been sadly lacking. The combination of all these approaches promises to make some inroads into the toll of proteinuric renal failure, but it is difficult to predict what their total impact may be. The main problem is making sure the treatment is not only available but actually carried out. Two studies by Terry Feest and his colleagues in Bristol, England demonstrate both the potential and the difficulties in this area [26]. This still leaves non-proteinuric disease such as polycystic kidneys. The genes responsible for this condition present formidable difficulties for manipulation by virtue of their size and reduplication, and genetic therapy for this disease must be some way off. Thus on the 30-year timescale I have imposed on myself, I cannot see the need for dialysis diminishing much, which may be good news for the dialysis industry but is bad news for patients in renal failure.

Envoi

The symbolism of end-stage renal failure in illustrating both the power of technology and the role of rationing in the treatment of disease have been treated only cursorily here. Another other major impact of long-term dialysis on patterns of care not treated here in detail was that of increasing the level and scope of nursing responsibility, which was pioneered in the treatment of end-stage renal failure in the 1960s. A full history of nephrology nursing has yet to be written, although a number of articles have appeared [2].

Lastly, and most importantly, it is 'easier to find out what was done than what was thought and felt'[28] and the perspective of patients and the impact on their lives which renal failure and haemodialysis produced [29–34] are little represented here, because only patients themselves can tell the story of what the dialysis experience involves. In the end the story of dialysis is the accumulated history of the hundreds of thousands of renal patients who have experienced it: but that would need another, different book which should to be written by those who experienced it at first hand, and it would be arrogant for a physician to pretend to this task. All those involved in the innovation and provision of dialysis have had their lives enriched by their contact, sometimes over several decades, with individual patients caught in the trap of renal failure and its palliative treatment. I have been one of this lucky group of carers, who had the pleasure as well as sometimes the pain of being able to participate in the transformation of a universally fatal condition into one which, if not treated, now can be palliated routinely.

Nor have I discussed here the major and increasing role renal patients themselves have had in determining the direction of political decision and medical action, through the pioneering of a partnership in medical care which was radical when it arose spontaneously in the 1960s (see Chapter 16). Throughout the world organizations of patients with renal failure and their relatives and advocates have grown up, and more and more governments bend their ears to what they have to say, although progress towards real autonomy of choice both from pressures of the medical establishment, government agencies and perceived commercial imperatives remains elusive.

In sum, for a halfway technology, dialysis has been not half bad.

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