A DISEASE AND ITS DEVICE

The Introduction of Dialysis for Acute Renal Failure, with particular reference to Leeds, UK, c.1945 – c.2000.

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ABSTRACT
The University of Manchester
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Doctor of Philosophy (PhD)
A Disease and its Device: The Introduction of Dialysis for Acute Renal Failure, with particular reference to Leeds, UK, c.1945 – c.2000
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Dialysis was the first instance of the possibility of replacement of organ function by a machine. Although now an established medical activity, it was only slowly adopted. The early machines were laboriously difficult in practice and appeared to have no clear indication for use. There was, however, a conjunction of this different mode of treatment with the identification of a disease suitable for its use: acute renal failure. The changing faces of dialysis and ARF form the substance of this thesis. The recognition of ARF and the concurrent invention of dialysis formed the basis and context for the specialty of nephrology. From this beginning grew a medical-industrial monolith in which the lives of hundreds of thousands of patients worldwide are supported by dialysis and transplantation at extraordinary cost – financial, personal, psychological, medical, and social. Dialysis and nephrology did not appear *de novo*, fully fashioned in 1960; rather, there was a gestation in the course of which not only did practitioners and their machine struggle for identity and acceptance but also the form and pattern of subsequent practice were established. It is these prodromal activities which are addressed in the first part of the present work which considers the founding of nephrology, the invention and dispersal of dialysis, and the role of the newly-defined condition of ARF in the conceptual framework of the specialty and as a motor for the adoption of dialysis technology. The intention is to provide a review of the secondary literature within an introduction for the reader of the three interrelated tropes elaborated through this thesis. Nephrological themes mirror much in the more general literature, particularly when comparisons are drawn with other specialities.

The establishment of the first British 'Artificial Kidney Unit' at Leeds General Infirmary in 1956 was a direct challenge to established medical opinion and a trigger for the development of nephrology and renal services in the UK, which briefly centred on Leeds. The Leeds story is taken to the early 1960s to illustrate how the emphasis in renal medicine shifted from the acutely ill patient to the lifelong maintenance of those with chronic disease. Again, Leeds here provides an example of global events. This redirected gaze is returned to in the final section, in which the tropes of acute renal failure and its technology continue in Chapters 7 and 8, which in a sense reflect Chapters 2 and 3 by considering the changes which accumulated up to the end of the 20th century. ARF in the 1950s proved to be the justification for dialysis. The technology continued to change, in part through commercial competition but mainly in response to new ideas and problems thrown up by changing practice. Late in the century, these technological modifications were re-applied to the treatment of acute renal failure. The disorder also changed over time, becoming an increasingly problematic fellow-traveller of techno-medicine as applied to a shifting patient population. Dialysis and acute renal failure provide a paradigm for late 20th century technology-defined, organ-specific medical specialisation.

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ABBREVIATIONS

AK	Artificial kidney
ARF	Acute renal failure
ASAIO	American Society of Artificial Internal Organs
ASN	American Society of Nephrology
CAPD	Continuous ambulatory peritoneal dialysis
CAVH	Continuous arterio-venous haemofiltration
CRCT	Controlled randomised clinical trial
CVVH	Continuous veno-venous haemofiltration
CRF	Chronic renal failure
ECG	Electrocardiogram
EDTA	European Dialysis and Transplantation Association
ESRD	End-stage renal disease (advanced chronic renal failure)
FDA	Food and Drug Administration, US Government
HD	Haemodialysis
ICU	Intensive care unit
IPPV	Intermittent positive-pressure ventilation
ISN	International Society of Nephrology
LGI	Leeds General Infirmary
MASH	Mobile army surgical hospital
MoH	Ministry of Health
MOSF	Multi-organ system failure
MRC	Medical Research Council (UK)
NIH	National Institutes of Health (USA)
NKRF	National Kidney Research Fund (UK)
PBBH	Peter Bent Brigham Hospital (Boston, USA)
PD	Peritoneal dialysis
SIRS	Systemic inflammatory response syndrome

1. THE SPECIALISATION OF NEPHROLOGY

> "Since the mid-1950s, specialization has become a fundamental characteristic of contemporary medicine, at the core of biomedicine's reliance on technology, fundamental biological research, multicenter clinical trials, and high costs."
>
> G Weisz (2006) p231

> "The history of nephrology, both as a body of esoteric knowledge and as a subspecialty, retraces in microcosm the recent history of what has become to be known as internal medicine. The history reveals increasingly refined science and increasingly specialized and subspecialized practice: a pathway from the general and the broad, to the highly defined and the restricted."
>
> S Peitzman (1986) p944

1.1 Introduction.

The thematic structure of this work precludes a straightforward chronological exposition: the specialty is regarded as a socioeconomic construct inextricably entwined with its diseases and technologies, shaping their history and in turn being shaped by them. Specialty formation is considered in terms of events which encouraged it and which enabled it to succour its technology. Conversely, when technology or disease are considered in detail, then also are aspects of specialisation invoked. The theme of nephrology is considered first because, although its genesis was dependent on and blended with the disease and the technology, the process and results provide a framework in which the contemporaneous naming of the disorder and acceptance of the technology occurred. Cameron and Peitzman write extensively on the foundation of the nephrology and the role of its technology. Both, but particularly Peitzman, foreground the division between academic science and clinical practice that has shaped the specialty as presently configured. This chapter draws extensively from their work, but broadens the context to consider wider political and economic factors and by positing illustrative comparisons with other divisions of medicine.

In this chapter, the separation of nephrology from general (internal) medicine is considered in relation to the literature on medical specialisation, and by reference to other specialties, particularly cardiology. The paucity of literature specific to renal medicine encourages comparison with cardiology, in which the development of the

specialty and its technology share a number of common features and which has a relevant literature of its own. Cardiology has been chosen as a comparator because it too is a thoroughly modern high-tech medical specialty. Its identifiable lineage is somewhat longer than that of renal medicine, dating as it does from the First rather than the Second World War. However, until the late 1940s the essence of cardiology was indistinguishable from general medicine, based as it was on observation and regimen. Nephrology and cardiology then came to exemplify late 20th century technology-based, interventional, academically distinct, high profile, high cost, self-defined and self-sustaining medical specialties.

It is conventionally, if somewhat deterministically, accepted that a condition exists which, once identified, requires a therapy and that this conjunction justifies a division of medical labour to manage and study both. This sequence also occurred in nephrology: mass wartime casualties brought a condition to the forefront of medical attention; coincidentally a therapy became available and appealed to some practitioners who conflated acute renal failure and dialysis into a sphere of activity recognisably different from that of the generality of the medical profession. An apparent anomaly within the foundation of nephrology was that its technological practice arm arose from surgery not internal medicine, yet was later sequestered by physicians.

Interest in the physiology and pathology of the kidney has a longer lineage than does the practice arm and this shaped the structure of the profession into which the events of the 1940s intruded, and in part determined the subsequent trajectory. Later events were conditioned by external influences, not least those in the USA following World War II. The academic, economic, scientific and cultural events in America are considered in depth because they provided an environment in which a specialty that was self-consciously 'modern', that is based on science and technology, could grow and thrive.

1.2 General context of the specialisation of nephrology.

1.2a Discourses of medical specialisation

Medical professional specialisation has intrigued social and political historians, sociologists, and health economists for at least 60 years. The parameters of thought for social historians of medicine were laid down by George Rosen's study of the separation of ophthalmology from more general surgical practice (Rosen 1944). The literature has since followed one of two paths: either wide-ranging analyses of specialisation in America and north-west Europe (Stevens 1998; Stevens 2003; Weisz 2006) or histories of the evolution of sub-specialties from which general conclusions may or may not be

made, closely following the pattern of Rosen's seminal work. The former category tends to be administrative histories of the broad divisions of medical practice, considering the factors that defined and perpetuated their structural organisation. This top-down analysis with an emphasis on the social structure and bureaucratic recognition of medical specialties results in a deterministic evaluation of specialisation[1]. The cited works almost invariably accept the inevitability of the fragmentation of medicine: the mass of medical knowledge is too great to be encompassed by an individual practitioner; individuals have differing skills, competencies and interests; society recognises and rewards different skills; new technologies are developed or adopted in piecemeal fashion; practitioners sharing intellectual or technical interests tend to congregate physically or by communication. It is then inevitable that specialisation occurs and this division within medicine is promulgated by social, intellectual, organisational, financial and personal power structures. The analysis is therefore of these structures and not of the original creation[2] of the specialties or of the divisions within the super-specialties.

Much of this deterministic view of specialism appears to follow the analysis of Beeson, an academic physician (Beeson 1980; Beeson and Maulitz 1988). He felt that specialisation within internal medicine was inevitable by the 1950s because of the quantity of relevant new information, diagnosis and therapy. The nidus for specialty growth had to be an academic setting wherein university-funded clinical scientists undertake intensive study of one group of diseases, resulting in new diagnostic procedures and special methods of management. These attract patients to teaching hospitals for tertiary care, which in turn justified the recruitment of trainees to learn and service the new protospecialty. Some trainees remain in academia, perpetuating the specialty structure, whilst others go into practice, treating selected patient groups. But there is nothing predetermined about the form that specialties have taken, especially when comparison is made across nations and health-care systems[3]. This analysis merely

[1] Weisz describes these histories as 'overdetermined': "…cast in the language of policy analysis, with the emphasis on current organizational problems and their solutions…specialization…presented as inescapable and clearly beneficial." (Weisz 2006, p xii).

[2] "Creation" implies that the origin of specialties and subspecialties can be fixed in time and space, which is patently not the case. No specialty arose *de novo*, all evolved into their current definition from a variety of starting points, with differing driving factors, and each with different, and rarely linear, trajectories.

[3] This is in no way meant to denigrate the significant scholarly achievements of these authors, but merely to exemplify what I consider to be a dichotomy in the treatments of the history of medical specialisation. Perhaps the apparent division is merely one of scale of perspective: broad overview of the social structure of specialisation versus a narrow focus on illustrative examples of subspecialisation. In the present work, the view is deliberately restricted, contingent and focused in subject, time and place.

recapitulates the actual post-war American model in which universities and academic-funding controlled the pattern and appearance of specialisation. This model is not necessarily universally applicable. In Britain and other fiscally-constrained countries, the appearance of organ-specific specialties was driven more by clinical practice and expediency than by academic largesse.

Georg Weisz comprehensively demonstrated that there is no single pattern of specialisation (Weisz 2006), whether viewed as broad categories (obstetrics, internal medicine, surgery, etc.) or as specific subspecialties. He further argued that the UK is exceptional in Western medical systems, and that this difference existed before and was formalised by the social construction of the NHS (Honigsbaum 1979). It is perhaps helpful to trace the chronology of specialisation within the medical profession as a whole before considering the subdivision of general (internal) medicine into subspecialties such as nephrology.

Gelfand, by limiting his argument to the tectonic divide between medicine and surgery (Gelfand 1976), suggests that gross specialisation became formally established in the 18th century. His concept of specialisation analogous to Adam Smith's division of labour (Smith 2008 (1784)) is based on areas of special competence within a relatively homogenous professional matrix. It is, however, self-evident that the division between physicians (learned, socially superior prognosticians) and surgeons (artisan performers of procedures) had been established from time immemorial and formalised in England from at least the Reformation. Other authors, including Rosen (Rosen 1942) and Weisz (Weisz 2003) have seen the 19th century as the period in which identifiable subgroups within the profession became discernible. Thus Rosen suggests that some surgical specialties (ophthalmology, otorhinolaryngology) were regarded as inevitable in the first half of the 19th century in the UK and in the latter part of the century in the USA. If this view is accepted, the socio-economic analysis of specialisation gains traction. At least in the UK, many of the aspiring surgical specialists were young, ambitious and denied status within the prestigious voluntary hospitals. In reaction, or by necessity, they established individualised clinics or hospitals in which they could pursue their limited expertise (Fraser 1964; Granshaw 1989). It may well have been this, rather than specialisation *per se*, which provoked the establishment resistance emphasised by Rosen. He considered that specialisation challenged the established mores of the profession and that this threat to the *status quo ante* provoked hostility, ridicule, ostracism and economic discrimination. Rosen's analysis has influenced most subsequent authors but

should possibly carry two caveats: a practical consideration and an acceptance that this narrative applies peculiarly to surgery and not to medicine or the overlap specialty of obstetrics and gynaecology. The practical consideration influencing the manifestations of surgical practice relates to technology. The rapid expansion of the surgically possible in the 19th century, aided and abetted by anaesthesia and antisepsis, resulted in procedures as disparate as colorectal and ear surgery, each requiring special instruments and techniques. Individual surgeons were not necessarily able to master and possess all the necessary technology and so, *pace* Adam Smith, became restricted in their field of expertise. This gelled with the administrative ambitions of powerful institutions.

As Weisz has indicated (Weisz 2006), general medicine made little progression during the 19th century and its claims to scientific status appeared fragile in comparison with surgery. However, by the 1880s specialisation was perceived in many countries as a necessity of medical science (Weisz 2003) because only specialisation permitted rigorous observation of many cases and enabled the collective desire to expand medical knowledge. Administrative rationality suggested that large populations, particularly of hospitalised patients, could best be managed through proper classification into appropriately staffed medical subdivisions. This way of practice emerged first and most powerfully in Paris and was widely adopted in continental Europe.

The division of medical labour was uniquely underdeveloped in the fragmented British medical community, where the complexity of medical specialisation was, as Weisz emphasises, dominated by the very British institutions of the Royal Colleges and the attitudes enshrined therein. Co-interested practitioners slowly formed aggregates within the colleges, but it was only late in the 20th century that these special interest groups split off to form their own specialty colleges, with their own programmes of admission, training and recognition. The colleges both framed and reflected the entrenched British distrust of the epithet "specialist". This attitude was only lately challenged from outside the profession, and even then in an unordered fashion. The belated acceptance of specialisation was precipitated by the division between hospital and general (primary care) practitioners, which was formalised by the professional arrangements negotiated at the inception of the NHS (Honigsbaum 1979).

Lloyd George's 1911 National Health Insurance Act did not cover hospitals, appointments to which remained predominantly honorary and determined by local boards. The elite hospital consultants had no need to think of themselves as specialists and, indeed, considered the soubriquet to be a restriction on their expertise and income.

The sharp administrative division between GPs and hospital consultants was formalised by the negotiated professional arrangements at the inception of the NHS[4]. Thereafter the development of specialism in the UK was, as Weisz contends, dependent on the personnel requirements of the NHS and not necessarily on professional aspirations. This opinion relies on an assumption of managerial strategic thinking not always evident throughout the NHS.

Post-NHS, the terms consultant and specialist became, in most people's minds, synonymous and interchangeable. The profession remained curiously reluctant to espouse change, the preferred term consultant 'with a special interest' remaining conventional usage for decades. As Rosemary Stevens has shown (Stevens 2003), the traditional mode of appointment at the voluntary hospitals (local, subjective, informal) became universally applied throughout the hospital service. Until late in the 20th century, there existed no definition of a specialist or of standards of training or experience required before appointment (or, for that matter, after): it was left to local institutions to decide whether a candidate was suitable in meeting their expectations.

The NHS introduced equal basic salaries for all consultants and funding for increasing numbers of junior staff, all with aspirations to consultant status. The financial and social pressures inhibiting sub-specialisation thus diminished, whilst at the same time there was an administrative drive to encourage particular expertise. The distribution of such specialists reflected the NHS structure: they were appointed on an *ad hoc* basis locally or regionally, and only occasional as a result of national planning.

In Britain, as elsewhere, the drive for specialisation in the latter half of the 20th century was primarily generated by the profession, only later achieving administrative approval. Weisz (2006) includes among the forces influencing and encouraging specialisation: medical research and education, professional strategies to monopolise specific domains, and trans-national sharing of knowledge and practice. These professional motivators became increasingly endorsed by the public, who equate specialists with the desirable attributes of expertise and science. Consultants practicing within a restricted region of expertise coalesced into like-minded groups, this social arrangement being endorsed by administrative structures and the Royal Colleges. Consultants in general medicine became somewhat redundant, so that by the turn of the

[4] The exception to this general discussion has been military medicine, in which specialisation was specifically encouraged during the two World Wars. Examples include orthopaedics in WWI, and plastic and thoracic surgery in WWII.

century only 2% of British physicians were classified as practicing general internal medicine, the remaining 98% occupying 28 narrow specialties.

Rosemary Stevens, Russell Maulitz and others have shown that divisions within general (internal) medicine have been as profound and significant as those affecting the profession as a whole (Maulitz and Long 1988; Stevens 1988). During the 20th century internal medicine fragmented into subspecialties, some of which feel that they are sufficiently distinct as to warrant recognition as autonomous specialties in their own right (if the hierarchical classification of medicine: specialties: subspecialties can be sustained in argument). The subdivision of internal medicine is relevant to the present work (Maulitz and Long 1988). All specialties, once the separation from general medicine or surgery has been set in train, expand their workload, and hence their power and influence. The process involves developing different and wider indications for their expertise and defining technology (aided and abetted by increasing commercial involvement) and by developing new disease categories, some arising from the identification of existing problems that can be brought under the aegis of the specialty, but others arising as a consequence of the specialty's particular treatment or technology. Specialisation within medicine is not static, but shows a tendency towards redefinition and fragmentation into sub-specialties, the intra-specialty sub-divisions usually being determined by the ownership of specific technologies. There appears to be no historical incident of the converse: the reaggregation of sub-specialties.

Nephrology does not differ from other organ-based specialties (the "-ologies") and utilised standard building-blocks: a single organ, the functions and dysfunctions of which may be studied with specific techniques, and a therapeutic technology requiring specialised manipulators. It follows that it is a doctor-defined category of medical activity. Nephrology was not defined by social criteria (age, gender, behaviour, etc.) such as have been used to separate the medical workforce concerned with geriatrics, paediatrics, gynaecology and so on. It was only after a significant number of nephrologists had come into being, and they had gathered a large cohort of patients with predominantly chronic renal disease, that a small coterie of paediatric nephrologists gradually separated from the main part of the specialty. This move, perhaps starting at Great Ormond Street and Guy's Hospitals in the late 1960s, seems not to have been led by nephrologists further specialising in children's problems but rather paediatricians developing a special interest in renal disorders. This super-imposition of a socially-determined subcategory of an organ-specific specialty was not without problems. The

ability to alleviate chronic conditions (for example, maintenance of life for ESRD patients by dialysis and transplantation) allowed children to live for many years, creating the social problem of the transition from childhood through adolescence to adulthood (Levene 2011). The potential conflict between the socially-determined and the medicalised subdividing of health care activity has received most attention in relation to the stresses between midwives and doctors attending childbirth (Donnison 1988), but is otherwise relatively unexplored.

Histories of individual (sub-) specialties take a bottom-up approach, showing that in many instances, specialties arose from the efforts and interests of practitioners, who joined with like-minded individuals to promote and defend their interests against but within the established pattern. These loose coalitions became more formally organised as they became more successful (an iterative process), the formal 'associations' eventually gaining recognition within professional and institutional structures and by regulatory or reimbursement authorities. During this stepwise progression from interested individuals to organised professional categories, the specialties acquired (by choice or external imposition) all the identifying hallmarks first enunciated by Rosen: a common body of knowledge, a recognisable corps of practitioners, an identifiable group of patients, a self-defining and self-perpetuating academic and professional structure, regulation of entry into the specialty, and eventually financial, legislative and organisational recognition within health-care systems. Specialty development and definition have been driven and maintained by doctors, not primarily by consumers or regulators of health care, who impact the situation only after a recognisable specialty has appeared.

In their endeavour to eschew 'Whiggish' history, historians of specialisation tend on occasion to play down the role of individuals. However, for the purpose of the present study, it is not unreasonable to at least consider the role of individual contributions to the foundation of a specialty. Except for practitioners in command economies or the military, there is and always has been a wide potential *choice* of specialisation. The literature contains little on what determines or restricts this choice; one might say the inherent or external factors determining career pathways. Inherent traits might include skills such as manual dexterity or spatial awareness, tendency towards high-risk or safe activities, self-awareness and/or self-promotion, personality 'types' that influence the desired level of contact with individual patients, and above all innate or developed 'interests'. External factors would include, but are not limited to, opportunities for training and promotion, selection procedures, and market forces. This apparent

digression, unsupported by an established literature, is relevant to the context of the present work in that this in part suggests that the actions of individuals had a significant impact on the establishment of nephrology as a specialty in the USA and Europe and, particularly, in the UK. The historian may find the who, when and where, but gaining an insight into the why and how is more problematic and for this there is little guidance from the literature, apart from obliquely in the medical sociology writings (Baszanger 1998; Fox 1998; Fox and Swazey 2002).

1.2b. Surgeons and physicians

A parallel or perhaps convergent, evolutionary pattern is in the changing ownership of interventional cardiology and nephrology between surgeons and physicians. The history of cardiac pacing has been extensively reviewed by Jeffrey, who showed that initially, pacing was necessarily an exclusively surgical occupation – insertion of pacing wires directly into the heart required major surgery (Jeffrey 1995). The introduction of transvenous pacing (by a surgeon) moved the procedure into the purview of physicians who perform diagnostic cardiac catheterisation. Physicians assumed that pacing then naturally fitted into the growing specialty of cardiology: "…the medical transaction included many new activities both before and after implant [of the pacemaker], and here the training of the cardiologist came into play…" (Jeffrey p618). Further: "…assumptions and standard practices…came up for renegotiation…as cardiologists…expanded the list of indications…[and] framed new conduction disease" (Jeffrey p612). Thus there was a logical (from the physicians' viewpoint) takeover of pacing, incorporating the acute procedure into the long-term management of the patient with heart disease. The transition of ownership of the interventional technology from surgeons to physicians was the same in nephrology, but the process and driving forces were different. With a handful of notable exceptions (in Boston and Paris), physicians exhibited at best indifference to dialysis for 10 – 15 years after its clinical inception. The antipathy to this active intervention has been characterised as emanating from an attitudinal divide considered in depth by Lawrence and others: physicians are "thinkers", surgeons "doers" (Lawrence 1985; Lawrence 1992; Lawrence 1992; Lawrence 1998). Peitzman invokes a conflict of ideas between the scientific elite physicians and the exotic pragmatism of surgeons tinkering in basements (Peitzman 1996; Peitzman 1997). At first, the most obvious cases of ARF arose in a surgical setting (trauma, postoperative, urology, obstetrics) and so surgeons experienced feelings of "desperation" (Warner 1975) to do *something* to relieve a perilous condition to the cause of which they

may have contributed. General physicians would not necessarily at that time have been confronted with the same sense of clinical immediacy. But experience eventually showed that dialysis was not a *deus ex machina*, but merely *part* of the *total* management of kidney failure, a truism firmly established when the therapy was applied long-term to the chronic patient. As renal physicians increasingly recognised and sequestered the care of renal disorders they became obliged to accept responsibility for the management of diseases progressing to end stage renal failure, the treatment of which is dialysis.

The movement towards the assumption of responsibility for dialysis lead to the creation of a subspecialty of hybrid physicians who did dialysis (Peitzman 1988). This division between physicians who treat and study renal disease and those who deliver dialysis persisted in the USA, reinforced by separate learned societies and journals, and a reimbursement system which encourages the provision of free-standing commercial dialysis centres: the division is sustained along both conceptual and economic lines. Although this division might appear to be an exclusively American phenomenon, it is echoed to a lesser extent elsewhere. The intra-specialty distinction between those who dialyse and internist-investigators has been present since the inception of a recognisable specialty of nephrology and was reinforced by the fact that a number of those involved in early dialysis were surgeons, not physicians, but the demarcation is fading[5]. On the other hand, the division in (American) cardiology has widened, with pacing having lately become a defined subspecialty with all the trappings of Board recognition, societies, journals, etc.: "[There has been] a de facto redefinition of pacing as a distinct field but one with strong affinities with cardiology" (Jeffrey p 619). It might be interesting to speculate whether future medical (sub-) specialty growth will follow the inclusive model of nephrology, where the technology is regarded as a tool, a part of the total management armamentarium, or the bifurcating model of cardiology where the technology is the defining feature. However, it may simply be a question of numbers and money: there are many more cardiologists, all with access to some revenue-generating procedure, so cardiology can accommodate a very broad church.

[5] Cameron 2002, p181: "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 was…'active' rather than contemplative and different from units mainly concerned with laboratory-based renal research…gradually this urological involvement with dialysis waned…leaving 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."

1.2c Journals and societies

As Lawrence says, formation of specialist societies and journals consolidates the development of specialties[6], by reinforcing professional identity and disseminating the specialist esoteric knowledge base. The early renal societies (Table 1.6) were not clinical associations but rather gatherings of scientists with an organ-specific interest[7], and this was reflected in the content of the journals (Table 1.7). This bias was probably significant in the rather slow diffusion of dialysis, as will be discussed later. It was certainly the reason for the early establishment of societies (ASAIO and EDTA) and their associated journals, which were orientated towards clinical nephrology, particularly dialysis, and were founded because of a sense of exclusion from mainstream nephrology as it was then structured. A further anomaly is the late appearance of American renal societies and journals. In part this was because not only did American clinical scientists publish exclusively in the well-established physiology and other science journals, but also because American general medical journals were receptive to clinical renal material, which thereby reached a wider audience than would otherwise be achieved by the monospecialty literature. The foundation of the American societies appears to have been, to say the least, stormy (Peitzman 1986; Peitzman 1988; Peitzman 1996; Peitzman 1997; Schreiner 1999; Peitzman 2001) and overtly 'political', a situation not unique to nephrology (Howell 1988). Nevertheless, the American Society of Nephrology immediately became the premier national society, annually attracting as many delegates from around the world as the quadrennial ISN meetings. The role of activists in founding specialist associations has received little historical attention, but must be of at least some significance to the understanding of the internal structure of the profession. The empirical observation that those who are most prominent in the establishment of specialist societies become themselves the 'establishment', the *de facto* leaders of the specialty, suggests that at least to some extent, altruism may not necessarily be their

[6] Lawrence 1985, p3: "…a specialized medical discipline, characterized intellectually by its orientation to a specific organ system, practiced by consultants, usually in hospitals, who control within their gravitational field the minor planetary bodies of any specialized medical solar system: journals, symposia, specialist books, learned societies, funding mechanisms, and so on."

[7] Cameron 2002, p179: "By 1950 there was a critical mass, at least from the 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 disease, the first of which was the meeting organized in London in 1953 by the newborn UK Renal Association and the CIBA Foundation." It should, however, be noted that only one paper at this meeting (by Alwall) was devoted to dialysis.
The first meeting of the International Society of Nephrology, in Evian in 1960, attracted 300 attendees, the third ISN meeting in Washington in 1968 was attended by 2134.

prime motivation. A final comment about renal journals is perhaps worthy of note: not only is there a disproportionate number of them but also a significant number (44% of the total) are not organs of specialist societies but rather the product of commercial publishing houses. This suggests that nephrology may academically and financially 'punch above its weight' in comparison with some other specialties.

1.3 Comparison with the specialisation of cardiology

1.3a. Introduction

With one or two exceptions, the creation[8] of nephrology has received little attention from medical historians (as opposed to autobiographical accounts by participants). The exceptions, who are physician-historians, have addressed this area but with an almost exclusively American bias. Whilst America was the nursery of nephrology, its cradle was in Europe, and the final product in America was in many ways distinct from that elsewhere in the industrialised world. It is probably self-evident that this distinction is the product of the unsystematic system of American health-care provision and its financial, commercial and reimbursement structure. The paucity of secondary literature may be partially circumvented by a comparison with cardiology, with which it bears some striking similarities and which has received significant historical attention[9]. Cardiology and nephrology are specialties arising from and sharing features with internal medicine and have significant parallels in their development, identity and consequences. Both arose from what had been minority interests in clinical and laboratory medicine up to the 1950s but became by the 1980s 'big ticket' specialties. Both developed or adapted diagnostic technologies which cemented their identity: ECG, echocardiography and catheterisation for cardiology; urinalysis, blood biochemistry (Kohler 1982) and biopsy in nephrology. Both came to be identified by iconic technologies (pacemakers and dialysis[10]), neither of which arose from existing mainstream practice but adopted non-medical technologies, and both of which received considerable public and media support and interest but professional resistance. To a geographically variable extent, the centrality of technology led to further specialty subdivision: 'invasive' and general

[8] Here used in the sense of being made from new or existing materials.

[9] "A growing interest in nephrology…could be classified schematically as being similar in emphasis to cardiology, both focusing on particular organ systems and being offshoots of internal medicine." (Stevens, 1998, p341)

[10] "And, of course, its [nephrology's] growth hormone was secreted by the dialysis machine" (Peitzman 1988, p211). "The implications of dialysis for nephrology as a subspecialty were staggering. Dialysis, with its opaque technical language, represented another element of the cumulating esoteric knowledge base of the discipline." (Peitzman 1988, p226).

cardiology, general nephrology and those who dialyse. Both resulted in radical changes in how medicine is organised and practiced. This is not to suggest that there has been a deliberate linear trajectory in either specialty, but rather that analysis of the analogies might provide an insight to the cultural, professional and technical environments that nurtured them.

1.3b. Early 20th century and World War I

The social history of medicine and warfare, as Cooter has shown (Cooter 1993), has received surprisingly little general analysis. The view that war is good for medicine may be unsustainable (Cooter 1990; Cooter, Harrison et al. 1999), apart from the advancement of individual surgeons. But the contrary view that warfare has a negative effect on the health of the population (Bourke 2003) is also open to criticism: analyses and opinions could be invoked to support either extreme. Warfare influenced the development of both nephrology and cardiology, the influence being either direct or tangential depending on contingent circumstance. Perhaps contrary to the perception that warfare results in little medical advance (Deutsch 1946)[11], wartime experiences had far-reaching effects on the two specialties. For cardiology World War I produced a still undefined syndrome ('soldier's heart') which became a major invalidity problem (Wilson and Carroll 1919; Lewis 1940; Howell 1998; Dyde 2011). Christopher Lawrence sees this period as part of the transition from 'old' to 'new' cardiology; that is to say from a pathology-based structural view of disease to one bringing to prominence the function of an organ, dependent on physiological precepts and the measurement of vital activity (Lawrence 1985; Lawrence 1985). Both Lawrence and Howell suggest that the Great War and its aftermath was the time when the secession of cardiology from general medicine began to take form. The military authorities assembled physicians interested in the heart, under the direction of Lewis and Mackenzie, to reflect on the medical, social and military aspects of this single organ-related problem. Informal contact between this common-interest group continued after the war and in 1922 was formalised as the Cardiac Club, which became the Cardiac Society in 1937, which in turn produced the British Heart Journal. Thus cardiology had an identity from like-minded clinicians assembled for a purely military purpose leading to a specialty organisation and publication.

[11] "The melancholy truth seems to be that wars generally have contributed but little to the progress of medical science. War undoubtedly does spread skills in medical practice as a result of the opportunities it gives doctors for operating on men in masses."

The ‘irritable heart of soldiers’ was a symptom-complex specific to combatants. Sufferers reported precordial pain, palpitations, shortness of breath, fatigability, giddiness, faintness and other symptoms which were felt to be indicative of a cardiac disorder. Wooley’s monograph (Wooley 2002), by assuming that soldier’s heart is an unchanging condition, traces its history from the American Civil War to WWI, following which it disappeared as a diagnosis. After WWI, 25,994 of the British army received pensions for heart disease, which would have included soldier’s heart (3,029 had kidney-related pensions). Between the American Civil War and 1914, various explanations for the symptoms were mooted by military medical authorities. Of interest is that from da Costa’s 1871 report on heart disease in the Union Army to the end of the Great War soldier’s irritable heart was considered to be a disorder of cardiac function, not structural pathology, precipitated by external events ranging from excessive exertion to ill-fitting tunics. Mackenzie in his cardiac textbook scarcely mentions soldiers’ heart, which he includes among functional disorders of occupations involving physical exertion (Mackenzie 1918).

World War I also revealed a kidney disorder prompting special enquiry (trench or war nephritis). The analogies and dissimilarities at that time between the disciplines of the heart and the kidney are sufficient to justify a longer discourse. Whereas cardiology has a relevant secondary literature, nephrology in this period has not previously been considered, so will be described in some detail and compared with soldier’s heart

In the spring of 1915, cases of a previously unrecognised kidney disease started to appear among the troops of the British Expeditionary Force in France (Abercrombie 1915; Anon 1915). This kidney disease was having an effect on the availability of troops fit enough for frontline duty. Research, however, was not directed towards treatment, which was not mentioned at all in the MRC report. Investigation was carried out along conventional clinical medical lines: detailed histological examination of material obtained at autopsy, clinical laboratory measurements such as estimating the amount of protein in the urine, and physiological experiments on convalescing troops. The nature of these experiments was entirely within current physiological thinking about the kidney. Investigators searched for a cause of this distemper by assiduously recording, testing and measuring in an attempt to discover a precipitating agent or event. These searches were constrained by both the available technology and by the then understanding of the potential causes of kidney disease: exposure to cold, malnutrition, metallic poisons, bacterial infections, drunkenness and dissolution, venereal disease, etc. That is to say,

the search was for an answer from a menu of known possible answers. The biochemical and other laboratory investigations produced lots of data (Brown 1916; Brown 1916; Wallis 1916) and excluded all known causes. The question of causation, and hence prevention, remained unanswered.

Even if the cause, nature and treatment of the disorder remained problematic, the Army and its advisors still had to decide on the practical issue of prognosis. Prognostic certainty informs decisions on invalidity discharges from active service and subsequent pensions. It became apparent that trench nephritis had a tendency to relapse, and these patients had a more serious prognosis as some did not recover. The non-resolving cases eventually progressed to chronic renal failure and death (Keith and Thomson 1918), confirming Osler's earlier gloomy prediction. This might be an instance of a 'new' way of practicing medicine (directed research to address a specific clinical question) being used to pronounce on 'old' medicine: an opinion based on the "incommunicable knowledge" of experience.

Trench nephritis and the 'irritable heart' were both perceived as problems significantly degrading the fighting efficiency of frontline troops and both placed long-term financial obligations on the state. They consequently achieved immediate prominence and the coordinated investment of resources, particularly intellectual, to a degree unthinkable in civilian practice at that time. Social contexts were thus attached to medical conditions, but the unidentified problems were considered to be soluble via a medical pathway: causation, diagnosis, prognosis and perhaps therapy.

Government agencies assembled distinguished medical advisors selected for their established interest in appropriate fields (for nephritis in renal physiology and pathology; for the heart in cardiac investigation). Their enquiries followed conventional lines: statistics of symptoms and numbers, physiological measurements, bacteriological and other laboratory investigations. These researches differed from civilian academic general medical practice only in the numbers of compliant subjects. Perhaps in the application of instruments to measure or record aspects of cardiac function did the methods employed differ from those widely available to interrogate any patient presenting with a challenging set of symptoms. However, the new technology was soon relegated to a subsidiary role, if not altogether abandoned. Experience showed that mechanical transcription of the heart's activity added little to that learned from traditional clinical observation, perhaps coupled with a programme of graded exercise. That is, the 'old' cardiology (Lawrence 1985; Lawrence 1985) proved in practice to be more effective in

this particular situation than was the 'new' functional[12] cardiology. Specifically, the new diagnostic technology did not materially augment the practice of the physicians then looking at the heart. Further, some of the strongest supporters of the 'new' cardiology and its instrumentation, particularly Lewis, abandoned the ECG and indeed the specialty of the heart (Howell 1984; Howell 1985; Howell 1988; Howell 1998). In his textbook on the ECG, Lewis makes no mention of soldiers' heart (Lewis 1920) and Mackenzie in his devotes but four of 500 pages to the ECG (Mackenzie 1918).

The combination of negative findings from both clinical and laboratory enquiries lead to the suggestion that soldier's heart was not a medicalised structural disorder but perhaps a manifestation of combat-induced anxiety (Mackenzie 1916; Wilson 1916) or, alternatively (but essentially the same), a disorder of the nervous control of the heart (Wilson and Carroll 1919). This resulted in a reconfiguration of its name and identity (restyled as effort syndrome or neurocirculatory asthenia) (Bound Alberti 2010), one effect of which was that soldier's or irritable heart did not appear as a diagnosis during WW II (Dyde 2011). As Dyde says, an increasing range of interpretations of a vague condition caused the profession to choose not to use the diagnosis at all, so that the number of cases fell dramatically. The symptomatology did persist as some aspect of a culturally-reconfigured disorder now called post-traumatic stress disorder (Jones and Wessely 2005), which also encompasses other WW I constructs such as shell-shock. In contrast, trench nephritis was throughout a structural, pathology-defined thoroughly medical disorder without any functional (somatisation) overtones.

The impoverished post-war British government was faced with many social and financial challenges, among which were 1.3 million war pensioners, at a cost in 1921 of £106 million (Howell 1985). The approach to heart and nephritis pensioners differed with different consequences for eventual specialty formation. The follow-up of the renal patients did not require any special competencies beyond normal practice and was delegated to routine Ministry of Pensions clinics.

For the more numerous cardiac patients, Lewis assembled a group of physicians to act as consultants to the Ministry (Lawrence 1985; Lawrence 1985). The primary

[12] Here we may be confronted with a semantic problem regarding the ambiguity of the word 'functional' in medical parlance. Functional may be used to encompass the efficiency of the working of an organ; thus damage to the myocardium will result in a functional deficiency (heart failure). Contrarily, functional can also mean the absence of demonstrable organic pathology to explain (to the doctor's satisfaction) a set of symptoms presented by the patient. The conflict between the medicalised desire for a measurable defect and the patient's experienced unwellness was illustrated by the recent pathology versus psyche debate on chronic fatigue syndrome (aka ME, yuppie flu, etc.).

responsibility of this group was to ensure that the invalidity assessors accurately differentiated structural heart disease from the functional, thereby reducing the invalidity benefit for soldier's heart. From 1922 these consultants, whose Pension role had ended, continued to meet together as the Cardiac Club. This essentially consisted of a dinner on the eve of the annual meeting of the Association of Physicians of Great Britain and Ireland. Lawrence suggests that the Cardiac Club was a step in the formation of cardiology, but Howell advises caution in this interpretation. There was no central theme, no unity of research, technology or practice. Fleming points out that of the original 15 physicians (all in their mid-40s) only 2 had been elected FRCP for more than two years (Fleming 1997). That is to say, they were relatively junior in the profession. They were all primarily general physicians and, indeed, six became professors of general medicine. Of the 19 subsequently elected to the club, four were eventually appointed to the staff of National Hospital. Among these was Paul Wood, who was to greatly influence the establishment of cardiology, as now recognised, in Britain.

Lawrence says that by the 1920s, cardiology in Britain was a respectable discipline with a coherent intellectual base. On the other hand, Howell points out that cardiology then fulfilled just two of Rosen's four criteria for the definition of a specialty. The big names, such as Mackenzie and Lewis, drifted away from the specific study of the heart. Indeed, Mackenzie advocated general practice as the only situation in which to gain an understanding of cardiology (Mackenzie 1919). The members of the Club were and remained general physicians who would have rejected the appellation of specialist. The same was true of all the attending physicians at the National Hospital for Diseases of the Heart in Soho, which although founded in 1857 was not then comparable in professional cachet with the National Hospital for Nervous Diseases, Queen Square. On balance one must conclude that, although there was continuity of intellectual interest in the heart, the inter-war status of cardiology bore little relationship to the separate specialty of the second half of the 20th century. The momentum for the post-WW II creation of the specialty of cardiology came largely from the USA, being carried to the UK by such as Paul Wood, and depended on new ways of interrogating and invading the heart. But even in the USA, heart specialists in the 1930s were predominantly general physicians. Thus Fleming highlights Frederick Price who confined his private practice to heart disease, but continued to edit his standard textbook of general medicine (Fleming 1997).

Laboratory investigation of cardiovascular or renal physiology (but not necessarily pathophysiology) persisted in some academic centres, particularly in the USA. This

provided the intellectual and conceptual framework that was adopted when the recognisable specialties eventually appeared. These studies were in the main conducted by non-clinician scientists and were not primarily directed at specific medical problems. The later clinical specialties seamlessly incorporated understandings from experimental physiology so effectively that it was "hardly perceived specifically as physiology at all" (Lawrence 1985, p33).

Although a narrative has been constructed positing that the Cardiac Club was a staging-post in the construction of the specialty of cardiology in Britain, one wonders (this speculation is based on the actual product of its members, individually and collectively) whether it functioned as much more than a companionable association of like-minded physicians. The practice and science of heart disease before and after the Second World War were as different in their essentials as were the activities surrounding the kidney. As Fleming says: "the era of the 'heart specialist', so dreaded by Mackenzie, did not dawn until after the Second World War" (Fleming 1997), as all of the exponents of cardiology prior to then were actually general physicians.

Cardiology and nephrology as presently constructed are paradigmatically late 20th century phenomena, their intellectual and practical content being entirely modern. Although taking elements from their antecedents, they are not directly based on what had gone before except to the extent that *some*, but only a very few, of those involved in ante-bellum organ-related practice espoused the changed activities that came to define the specialties. If Lawrence's 'old' and 'new' cardiology of the early 20th century are to be accepted (and this has been at least in part questioned by Howell and others), then to these must be added 'newest' cardiology to separate the specialty as it now is: technological, interventional, divorced from general medicine, self-sustaining, accepted by professionals and lay persons alike. Nephrology and cardiology may be said, in retrospective analysis, to have evolved from earlier medical thought and practice. But subsequence is not necessarily consequence and the identification of two similar organisms does not prove evolutionary sequence. It may be said that in the specialties, the dissonances with the postulated antecedents outweigh any commonalities.

1.3c World War II and later conflicts

Conflicts after World War I had little direct effect on cardiology. Cardiothoracic surgery was, however, stimulated during WW II by the realisation that penetrating wounds of the heart could be successfully operated (Hurt 1996). Rapid surgery within the heart itself paved the way for valvotomies and other more daring procedures, the

complexity of which increased as life-support technology was developed in the post-war era. The impact of this adventurous surgery on cardiology was to demand more accurate localisation of potentially operable lesions and the development of pacemakers, in part to rectify post-surgical problems.

Nephrology on the other hand was profoundly influenced by both WWII and the Korean conflict. Acute renal failure, which was to become the defining condition for interventional nephrology, was rediscovered in 1941 as the "crush syndrome" by a physician who became a rheumatologist (Bywaters and Beall 1941). As will be elaborated in the chapters on ARF, the crush syndrome was not a new disease but instead a dramatic highlighting of a previously low-profile entity. Specifically, ARF following trauma or crushing had been described in the German literature of the Great War, where it had passed unnoticed by the Allies. Prull, considering British and German pathology services in the 1914-18 conflict, shows that the attitudes and endeavours of the medical staff reflected their cultural-historical situations (Prull 1999). British pathologists, the product of a more liberal political society and education, concentrated on the clinical pathology of the living and integrated their work with other medical and surgical disciplines. Their output was consequently predominantly related to bacteriology, hygiene, etc.. In contrast, German pathology was a hierarchical product of the rigid societal structure of Wilhelmine Germany. Under the direction of Aschoff, their effort was concentrated on what was essentially pathological anatomy. The high autopsy rate proved of little military use, but did coincidentally define the pathology of ARF.

In the Second War, the Allies showed much more interest in ARF and further clinicopathological research on post-traumatic and other ARF, much of it in a military context (Maegraith, Havard et al. 1945; Lucke 1946), meant that by the end of the war the clinical syndrome and its causes had been delineated and widely recognised. That a previously unrecognised but dramatic condition rapidly came into medical awareness was probably due to a marked increase in its frequency – large numbers of civilian and military casualties resuscitated sufficiently to survive to develop ARF, exposure of large conscript armies to tropical diseases such as malaria, and new nephrotoxic therapies such as sulphonamides. This gave interested doctors a disorder on which to deploy their technology, that is to say the specialty of nephrology as now configured was grounded on a condition described in wartime.

The relevance, if any, of war on the invention and introduction of dialysis is debatable. In the mid-1940s dialysis was simultaneously but independently invented in

occupied Holland, neutral Sweden and in Canada, which although heavily committed to the conflict was geographically and culturally far distant from the theatres of war. Warfare may have inhibited the construction and distribution of dialysis, both the machines themselves and the knowledge of the technology. The evidence, however, is that the slow adoption of dialysis was primarily due to doubts about its efficacy and anyway Kolff and others published in widely-available Scandinavian English-language journals. Reaction to Armageddon could well have encouraged post-war pan-European scientific discourse and cooperation, embodied in the EDTA and internationally in the ISN. Post-war American optimism, even triumphalism, certainly fostered investment in biomedical science, from which nephrology was a clear beneficiary.

That warfare gives doctors the opportunity to treat large numbers of patients (Deutsch 1946) is illustrated by the Korean conflict, during which incontrovertible evidence that haemodialysis actually saves lives of patients in ARF was adduced (Teschan, Post et al. 1955). Again this was the result of circumstance: the US military sponsoring research and development in dialysis when American academic centres were largely ignoring it; and the Korean War was the first time that *stored* blood was used in resuscitation, resulting in the unpredicted and potentially fatal complication of hyperkalaemia, a condition eminently responsive to dialysis (Cameron 2002).

1.3d Dialysis and pacemakers

The specialties of cardiology and nephrology are defined by their technologies: nobody other than cardiologists insert pacemakers, nephrologists prescribe and manage dialysis[13]. Both pacemakers and dialysis arose outwith the esoteric knowledge base of the protospecialties, outwith the recognised centres of teaching and expertise and were developed by young non-established practitioners. Both demonstrate that the *invention* of an effective intervention does not necessarily require an accurate knowledge of disease causation: empiricism rather than science can work. One unforeseen consequence of the successful introduction of interventional technology was the rapid acceleration of the reductionist approach to treatment. Prior to the use of the devices management of cardiac and renal patients was, for want of other options, altogether more

[13] Cameron 2002, p181: "It is almost certain that the introduction of dialysis was an important motor which accelerated the emergence of nephrology as a specialty. 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."

holistic, depending as it did on an almost Galenic regimen of domiciliary diet, rest and exercise. Technology provided the key for the easier entry of reductionist laboratory clinical science into the management of specific patients (Lawrence and Weisz 1998).

The introduction and development of pacemakers and haemodialysis show coincidental synchronicity. The invention and clinical use of prototypes of both in the 1920s and 1930s was unrecognised by the wider medical community, and clinically usable devices arose in the immediate post-war period. While pacing was an American invention, dialysis was innovated in Europe but received no acceptance until it was adopted, developed and promoted in the USA. Much has been written about the optimistic, unregulated, hospital-based, prosperous, technology-orientated atmosphere of post-war American medicine which favoured the entrepreneurial implementation and promotion of new ideas and techniques (Stevens 1989). The media and public were receptive to science (seen as 'machines') as a cure for all ills, and this unquestioning positive attitude encouraged the advocates or sponsors of new medical technology. The unregulated environment of the 1940s and 1950s allowed that diffusion and development could proceed synchronously; practitioners had a high degree of autonomy and were thus able to justify their actions (if ever called upon to do so) on the basis of experience or benevolent intent; controlled randomised clinical trials were virtually unknown and had certainly not impinged on the surgical consciousness; there was little or no ethical oversight. Government regulation of devices did not appear until much later (1976 for the FDA to receive powers to regulate innovative technology), by which time both procedures had become firmly established as routine and embedded as part of normal practice. American and British device legislation precludes retrospective assessment of established practice. It was only later that any challenge was made, and then the devices and procedures *per se* were not questioned, rather their social, financial and ethical consequences.

Whereas the general social atmosphere may well have been critical in promoting therapeutic experimentation, at least for dialysis and pacemakers innovation was a very personal and individualistic affair. In later years both Alwall and Kolff repeatedly stated that they were (independently) motivated to invent dialysis, and Thorn to develop and promote it, by a feeling of helplessness when faced by a particular untreatable patient. Kolff and Zoll (for pacemakers) used individual case histories to promote their devices (Heiney 2002). (In retrospect it is surprising that the Kolff rotating drum became the iconic dialysis machine as it was less sophisticated and harder to use than its

competitors; however Kolff was a very active 'champion' of his device, while Alwall was by nature reticent and Murray was a surgeon who rapidly lost interest and turned to other endeavours (van Noordwijk 2001; Cameron 2002)).

The first dialysers and pacemakers faced two major problems inhibiting their acceptance: limited clinical indications and unsuitability for long-term use. The pacemaker was introduced for the treatment of a rare condition (Stokes-Adams attacks due to complete heart block) and was a cumbersome device only suitable for the acutely ill, bed-bound hospital patient: "…to all but its sponsors, pacing…had the look of an interesting but distinctly marginal new technology…" (Jeffrey 1995). Although the "pioneers" of dialysis had envisaged it for the treatment of chronic renal failure, it rapidly became apparent that one or a few treatments merely temporarily postponed the inevitable demise of patients with chronic *irreversible* uraemia. Repeated long-term dialysis was simply not feasible. However the ground had been prepared for the acceptance of both technologies. By the 1940s, the heart had come to be regarded as an electromechanical device (and hence amenable to electrical interference) and, further, complete heart block was the "ideal" electrical failure – it was definable clinically and by ECG, it produced dramatic symptoms and death, and it could be managed by a more or less straightforward device. Similarly, among the very first patients to receive dialysis were some with a newly-recognised syndrome of acute *potentially reversible* renal failure, and this minority clearly benefited from dialysis which could support them through the short period until natural recovery of renal function. Thus dialysis was also applied to a numerically restricted group of patients in whom its benefits could be clearly demonstrated.

It required additional coincident specific events to "prove" that both pacemakers and dialysis were acceptable treatment: the results of dialysis in Korea and the recognition and treatment of post-surgical heart block (Jeffrey 1995). Advances in other specialties had enabled the start of the surgical correction of congenital heart defects in the mid-1950s. However, some 10% of the children were left with potentially fatal heart block following surgery. To counter this, Lillehei implanted pacing leads into the heart muscle during surgery (the first implantable flexible Teflon-coated leads) which solved the problem. However, pacemaker 'boxes' were large and required mains electricity and were thus unsuitable for permanent ambulatory care and vulnerable to power failure. Lillehei 'consulted' an electrical engineer who came up with a portable battery-powered transistorised pulse generator. Two consequences ensued: lifelong pacing for chronic

conditions became feasible and the electrician founded Medtronics, which remains the market-leader in cardiac electronics. Soon after, Belding Scribner in Seattle had liaised with an engineer, who also utilised new technologies from outside medicine, to create the 'shunt' which allowed long-term repeated vascular access for the dialysis of chronic irreversible renal failure[14](Cameron 2002).

The technical ability to provide 'permanent' treatment opened up a potentially huge market (the number of patients on dialysis or with implanted pacemakers in the USA is similar at ~1 million), a market which attracted commercial and governmental investment, which was reinforced by the 'discovery' of further indications for the use of the technologies: widening age-span of patients, identification and understanding of 'new' arrhythmias amenable to pacing, earlier institution of dialysis, the return to dialysis of failed transplants, the use of renal support therapy for non-renal disorders such as severe sepsis. A liberalisation of funding through Medicare (1965) caused further increase in numbers of patients – a tripling of the pacemaker insertion rate in the USA. The Social Security Amendment of 1972 had an even more dramatic impact by making dialysis freely available to all US citizens (Rettig 1991) and amply remunerative for the providers. This landmark amendment of Medicare provision provides the clearest demonstration of the manipulation of legislation by interested professionals and powerful lobby groups. Such was the demand released that the Federal authorities sought to control expenditure by the 1983 amendment of Medicare, which was specifically directed at the fiscal impact of cardiac and renal services.

The explosion in the numbers of chronically supported patients had consequences not envisaged by the 'pioneers' of the treatments: a huge increase in the number of certified practitioners and the development of ambulatory outpatient facilities. Both dialysis and pacing evolved from hospital-based acute activities to an entirely outpatient setting, requiring a re-think on how medicine is administered and provided. These specialties were the first to move technology outside the hospital ward. The care of these outpatients was increasingly devolved from doctors to technicians, who care for the machines. In both cardiology and nephrology, the patient has been further distanced

[14] Cameron 2002, p181: "Then, in 1960…, long-term dialysis became possible. Within five 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."

from the hospital (and its physicians) by telemetry for pacing, and home dialysis. In both, doctors initially treated both patient and device (often actually building the latter), now to a great extent the medical care is directed towards the complications of long-term survival *on* the device, which successive commercial refinements have made largely self-sufficient.

1.3e Diagnostic technologies.

As cardiology developed the ECG as its central and defining instrument (Bynum, Lawrence et al. 1985), so nephrology also obtained a diagnostic procedure which required both enactment and decipherment by the specialist. The percutaneous renal biopsy, obtaining a fragment of living tissue by means of a hollow needle, was in fact an adaptation of a procedure introduced for the investigation of another organ. The gradual adoption of the renal biopsy through the 1950s and 1960s had many consequences, all of which further refined the specialty (Cameron and Hicks 1997). Biopsy is a procedure requiring practice and expertise and hence not only generated a perceived need for renal specialists but also allowed those specialists to attract trainees who could be taught the art. By allowing examination of tissue from living subjects, biopsy could reveal the natural history of conditions previously known only from their terminal appearance, or unknown because they had not been manifest in autopsy material. This meant that the earlier certainties about intrinsic renal disease, as enunciated by Bright or Ellis, became redundant. What had previously been quite simple and straightforward became the complexities and uncertainties challenging the nascent specialty. The newly-acquired ability to sample living tissue with a cutting-needle and then to subject it to painstaking pathological analysis (including, according to Peitzman, the first routine use of the electron microscope in clinical medicine) represented, in Peitzman's words "a thoroughly high-technology way to look at the sick kidney" (Peitzman 2007, p97).The rebuilt nosology both influenced specialist treatment and also redirected academic enquiry back to the deranged kidney itself (Peitzman 1989; Peitzman 1992). Biopsy, by "subdividing nephritis and nephrosis into an intimidating menu of new entities" which "added many bricks to the structure of esoteric knowledge which could house a renal subspecialty" (Peitzman 1988), had the predictable consequence that knowledge of renal disease became too arcane for the general physician. He eloquently points out (Peitzman 2007), the esoteric language of renal disease may foster communication and cement

relations between the cognoscenti but can only cause bewilderment to the patient and even the general internist[15].

Cameron is even more convinced of the centrality of the renal biopsy in the genesis of nephrology (Cameron and Hicks 1997). Reflecting his own considerable experience, he reports that at first many pathologists were suspicious of the tiny fragments of tissue obtained by needle biopsy, so the budding specialists in nephrology had perforce to become expert in the interpretation of renal histology. Alone of the various commentators on the history of nephrology, Peitzman (2007) suggests that initially some criticised percutaneous biopsy as potentially dangerous, but that medical freedom and autonomy ("a sense of adventure and license", p97) at that time allowed the rapid assimilation of the procedure into the specialty armamentarium. At the risk of hyperbole, Cameron says: "If in the Middle Ages, the symbol of the physician was the matula full of urine and in the 18th century, the gold-headed cane, in the middle part of the 20th century, the symbol of the nephrologist was the biopsy needle in his or her pocket. Usually, this was a personal possession…" (p356).

The argument is sustained by considering the effects of later changes in biopsy technology. The widespread sampling of tissues from anywhere in the body by all sorts of specialists stimulated the commercial development in the 1970s of disposable needles, of which the "Tru-Cut" (Travenol) was by far the market leader. These were considerably more efficient than their rather cumbersome predecessors and proved remarkably effective when used with organ location by ultrasound, a radiological procedure also coming into general use at the same time. An entirely logical commercial development was to combine a mechanically-triggered needle with an attachment for the ultrasonic probe to create the biopsy 'gun'. This gave increased safety and high precision, but generated conflict between radiologists (who owned ultrasound) and nephrologists (who felt that they owned the needle). The contested division of labour was felt most keenly where the performance of a renal biopsy not only meant additional remuneration but also provided an emblem of identity for those nephrologists not practicing dialysis. Cameron (1997) encapsulates this changing identity of the specialty: "This ethos was eroded first by the introduction of disposable biopsy needles…and then by biopsy guns…However, it is interesting to see how violently the nephrological

[15] "The situation is made worse by the lack of any available sort of story of cause and effect. For the majority of these biopsy-diagnosed successors to Bright's disease, the cause is unknown, at least in the sense sought by patient and doctor." (Peitzman 2007, p99) That is to say, the term 'idiopathic' (i.e. causing itself) provides no useful information, but is remarkably acceptable to the specialist.

community has reacted to the perceived 'threat' of interventional radiologists doing guided renal biopsies by biopsy gun using ultrasound control, just as they do in almost all organs and tissues of the body…The strong reaction is not just a matter of lost financial reward – losing control over renal biopsy strikes at the unconscious sense of identity of nephrology."

That such importance should have been attached to this tussle for control of a procedure is indicative of its centrality to the identity of the specialty. When the disagreement occurred (in the 1980s) nephrology had become well-established, indeed powerful. It is unlikely that actually doing biopsies featured high in the list of activities of the leaders of the specialty. Further, the importance of the biopsy lies in its product: the interpretation of the appearance of the obtained tissue and the actions which flow from this. This remains exclusively in the purview of the nephrologist. Nevertheless, to many renal specialists the biopsy remains iconic.

By way of contrast, cardiology early lost its monopoly of the ECG. Commercial development of the instruments rendered them not only compact, efficient and user-friendly but they also gained increasing sophistication, for example automated pattern recognition capable of providing diagnoses. Thus the diagnostic procedure became the property of all and sundry. Cardiologists, secure in their own identity, did not obstruct this but actively encouraged it.

The history of the study of the kidney and its malfunctions could alternatively be portrayed as the history of biochemistry (Kohler 1982). The kidney, because of its readily accessible product, was the first organ to be chemically dissected and much of 19th century medical laboratory work related to the kidney and associated enquiries such as osmosis. As discussed elsewhere, urea was identified early in the 19th century, but measurement of essential cations (sodium and potassium) proved difficult. Assays were unwieldy, imprecise and time-consuming (up to 48 hours) and required large volumes of biological fluids. By default, experimenters and clinicians resorted to measuring anions, assuming (usually incorrectly) the equivalence of chloride and bicarbonate. This lack of accurate, rapid estimation of sodium and potassium resulted in general ignorance of their clinical significance and also restricted academic research. The development of technology for rapid accurate biochemical estimation was essential for the understanding of kidney disorders, stimulation of research and, most importantly, for the safe implementation of dialysis (Peitzman 2010). Of all the electrolyte disturbances of renal

failure, raised serum potassium is the most acutely dangerous, with levels greater than the normal range resulting in cardiac arrhythmias and death.

Rapid estimation of blood potassium levels was not possible prior to the development of the flame photometer, first invented in the 1920s in Germany but not introduced into clinical practice until the work of Phyllis Hald at John Peters' laboratory at Yale (Hald 1947). Prior to this, but published later and unknown in the USA, Ruud Domingo had first clinically applied the flame photometer in association with Kolff (Domingo and Klijne 1949). Domingo was an agricultural scientist using the flame photometer (he had modified a Zeiss instrument to measure *both* sodium and potassium) to monitor salinity in the reclaimed polders around Kampen (Cameron 2002). As part of his involvement with the Dutch Resistance, Kolff provided Domingo with picric acid to make him appear jaundiced and thus obtain an 'Ausweiss', the medical certificate exempting him from forced labour and deportation. The trade-off was that Domingo applied the procedure to samples from Kolff's renal failure patients some years before the technique entered mainstream medical practice (Heiney 2002). In Britain, home-made photometers were in early use at University College and the Middlesex Hospitals (Spencer 1950; Baron 1951) and the technology entered clinical service through academic departments.

Peitzman (2010) regards the flame photometer as a motor driving the establishment of nephrology because of its utility in both academic research and in clinical metabolic diseases. He shows that it was fundamental to the definition of obscure electrolyte disorders, such as Bartter's syndrome (Bhandari and Turney 1998), the complexity of which helped to establish nephrology as a distinct intellectual activity removed from the routine of general internal medicine. Cameron goes further, stating: "It is difficult to see how acute dialysis could have continued had some technique of electrolyte analysis applicable to the clinical setting not become available" (Cameron 2002, p116). This opinion was endorsed by Frank Parsons, who was adamant that without the prototype commercial flame photometer (EEL Electronics, Cambridge) that was made available to Pyrah's metabolic research unit at Leeds General Infirmary, it would have been impossible not only for him to perform his metabolic research but also to have initiated dialysis (Parsons 1989). Quite simply, potassium (and to a lesser extent sodium) levels became key to assessing both the need for dialysis and for monitoring the rapid shifts in electrolyte levels during treatment which, if not detected quickly, were potentially very dangerous. The flame photometer fulfilled the requirement for the prompt estimation of levels in small samples of blood: analysis and therapy could be synchronised.

The utility of the flame photometer in both research and practice encouraged sequential refinements in academic centres which were taken up by electronic companies. A step-change not only in the role of the instrument but also in the relevance of biochemistry to clinical practice occurred when Leonard Skeggs incorporated a flame photometer into his automated multichannel analyser (Skeggs 1957), which was further developed in cooperation with the Technicon Instruments Corporation (Isreeli, Pelavin et al. 1960). The resulting automatic sequential multiple analyser, capable of rapidly and accurately producing a print-out of chemical analyses of small blood samples from many patients, revolutionised hospital medicine from the late 1960s (Skeggs and Hochstrasser 1964; Skeggs 2000). The Technicon multichannel (SMA12) print-out gave all the results necessary to manage metabolic (essentially renal or hepatic) derangement. No patient escaped without having a 'profile', usually performed daily. Medicine had been reduced to numbers and normal ranges, and never looked back.

Rather than the flame photometer, and the subsequent biochemical analysers, being the engine of nephrology as suggested by Peitzman, it is perhaps more accurate to view them as enablers facilitating the practice and science of the specialty. The ability to measure blood constituents rapidly and accurately eased the development of, and comfortably fitted into the ethos of, the specialty in both its academic and its practical aspects.

Cardiology and nephrology are high profile specialties within internal medicine. Their evolution appears to be parallel and synchronised, but this a deception because their developments have arisen in only small part from internal motors, but in large part from shared external circumstance. The external forces are the common factors; the internal properties are the confounding factors[16].

[16] In what is essentially a personal memoir (Schreiner, G. E. (1999). "Evolution of nephrology: the caldron of its organizations." Am J Nephrol **19**: 295-303.) rather than a true history, one of the key players in the establishment of American nephrology summarises its history thus: "Nephrology was the first of the new medical specialties to emerge in the reconstruction after World War II. It was a novel fusion of disparate elements of basic science, particularly physiology, the development of clinical tools to understand and treat renal disorders, dedicated physicians applying science to clinical syndromes, and the desire of philanthropic people to associate for needs not met by the medical organizations then dealing with renal disease. It was formed in a caldron of revolutionary changes in medicine, biology, and the social order. Its evolution broke down old barriers that had prevented a unified, complex, multidisciplinary approach needed for the delineation of renal pathophysiology, the rational design of therapy and the bold step of renal replacement. The organizations that helped nephrology were themselves built in fits and starts. There were blind alleys, and not all participants knew the eventual outcome." (p295).

1.4 Intensive care as a comparable boundary case

A partial, but potentially illuminating, contrast to the nephrology/cardiology juxtaposition is provided by assisted respiration (ventilation) and intensive care: the analogies and dissimilarities perhaps demonstrating that the route to medical specialisation is neither predetermined nor linear but is rather the product of circumstance. The utility of intensive care for comparison with nephrology resides not only in the dissimilarities between the two in the 1940s to 1960s, but also in the later convergence of the specialties which led, from about the 1980s, to a different form of ARF, treated with a different technology. This procession provided the rationale for the socially-determined reconfiguration of the specialties, as will be later considered in relation to the transmogrification of disease and machine.

It is arguable that assisted respiration existed and exists in isolation from a recognisable medical specialty, and that intensive care is an organisational convenience to manage and control technology, which by default rather than design has largely come into the ownership of a particular group of practitioners (anaesthetists, from whom 'intensivists' have at least partially split). Assisted respiration arose as a deliberate engineering solution to a specific, limited but emotive medical problem: respiratory muscle paralysis due to epidemic poliomyelitis (Maxwell 1986). Although a partially successful supportive therapy existed (Stanton 2000), the 'iron lung' did not arise from a nascent medical specialty and, indeed was entirely independent of (intermittent positive pressure) ventilation employed by anaesthetists for short-term operative support. The pivotal event was the recognition that this treatment was inadequate for the numbers and complexity of the acutely affected patients in the 1952 Copenhagen polio epidemic (Lassen 1953). The solution was not technological development but rather the utilisation of an existing technique (IPPV) managed by a specialty outwith internal medicine. As Wackers confirms, IPPV was born of necessity and immediately relegated the iron lung to a museum piece (Wackers 1994). It was introduced by a practitioner (Ibsen) who knew nothing of poliomyelitis but who effectively applied what he had learned to do in the operating theatre. No complex statistics were required to prove the effectiveness of the innovation, there was immediate self-evident visible proof. But, beyond this dramatically effective treatment, there were long-lasting implications: old truths (cognitive, technical, social) were instantly broken down, developments which had already started were accelerated and new lines of research were initiated. By deploying anaesthetic skills for a medical problem, it became apparent that IPPV facilitated the

management of other medical patients requiring prolonged anaesthesia and paralysis: initially for tetanus and then gradually for other organ failure. As this treatment was not infrequently an extension of the operative recovery room, it appeared appropriate for anaesthetists to manage it, a situation reinforced by the apparent centrality of ventilation in intensive care (itself defined by the use of ventilators, which are the most obvious of the many pieces of equipment). Grouping of patients requiring this labour-intensive treatment into discrete sites had obvious management benefits but also the 'separateness' enhanced the aura of ICUs and strengthened the power and ownership of the practitioners.

This reading of the history of intensive care derives largely from physician-participant recollections (Stanton 2000; Stanton 2005), supported by histories in which technology and individuals have centre stage (Hilberman 1975; Young and Sykes 1990; Berthelsen and Cronqvist 2003). Thus the history of intensive care could be portrayed as analogous to nephrology: a technology which defined practice and medical separation. This determined progress has been challenged by social historians who see intensive care as the product of wider socioeconomic contexts in which practitioners and technologies are but players. Fairman makes the case that ICUs are a consequence of the role of the nurse, portrayed as intensive observation and triage, for which traditionally they have gathered the sickest patients together to optimise nursing care (Fairman 1992). Stanton (2005), resting on Fairman's work, calls this "a logical clustering of patients requiring the most nursing surveillance." Adducing evidence from detailed case studies of Philadelphia hospitals (Fairman 1999; Fairman 2000), she develops this thesis by showing that ICUs arose in response to economic and organisational demands which sought optimal deployment of a scarce resource: competent trained nurses. A recent essay (Bulander 2010) also sees this managerial solution to the mismatch between the availability of scarce nursing labour and the increasing numbers and complexity of critically ill patients as central to the development of the concept of ICUs. Bulander says that the ICU, the totemic emblem of the modern hospital, was "defined and understood not by a particular style of medical practice or by particular medical devices, but by the presence of nurses in an organisational environment that allowed them to concentrate on bedside patient care." He further says that "technological advancement and physician specialisation were late-comers to the ICU environment" (p 636). Indeed, Ibsen himself admitted (Ibsen 1966) that congregating the polio victims receiving IPPV in Copenhagen was an attempt to maximise the efficacy of available resources. Stanton (2005)

encapsulates the formation of ICUs as "an arrangement of space and allocation of care, as much as a matter of technological innovation."

It would therefore appear that the space and staffing of the "administratively distinct clinical units commonly called intensive care units" (Hassett 1984) preceded the complex technology now contained therein and the specialisation of the doctors who practice there. ICUs are now defined by equipment and by the intensivists, but were not always so. The spatial and workforce arrangements constrained by socioeconomic factors contrast with the chronology of nephrology, in which the technology and a specific disorder were the stimuli for specialisation. Individual specialists gathered a team of nurses and technicians to care for the machine and its supplicant clients, the organisational allocation of space and division of labour followed this and was formalised into (physician-managed) renal 'units' as a result of later technical sophistication and rising demand.

Perhaps beginning in the 1960s, ICUs and renal units, if considered as functional spaces, followed similar pathways determined by commercial technical development and the separation of staff into professionally specialised cadres. Similarities are unsurprising as the scope for organisational innovation in the late 20th century acute specialties was constrained economically and socially. Thus intensive care and renal units spread rapidly but unevenly (Stanton 2005) so that every acute hospital worldwide had a site of activity equating to an ICU by the end of the 1970s at the latest. What differed geographically was the quantity (usually expressed as a ratio of total hospital beds) of ICU provision: a source of political and professional friction in fiscally-limited health services such as the NHS. The debate over the provision of dialysis services was also highly charged, perhaps because of its clear identity in the public mind and the advocacy of patient groups and the media, which has not generally been a feature of ICU-related contests over resource allocation. Both activities became extraordinarily costly and inexorably consumed ever increasing resources, predicated on ever increasing demand from an ageing population experiencing complex medical problems. Both ICUs and nephrology are embodiments of increasingly adventurous medical and surgical interventions in an expanding vulnerable patient-base.

Both specialties became more and more technology-driven with the blossoming input of the medico-industrial complex as demand enlarged the market. An example of

continuing analogies is the introduction of computerisation of the basic instruments[17] of the specialty. Nursing staff in ICUs became overwhelmed by the volume and complexity of the data emanating from the machines progressively introduced to continuously monitor patients' vital functions. If ICUs are an organisational arrangement predicated on the need for intensive nursing surveillance, then they fall at the first hurdle if the quantity and quality of the observational information exceeds the nurse's ability to comprehend and respond appropriately. The introduction of increasingly numerous and sophisticated monitoring devices resulted in just such a situation. The adopted solution was computerisation, from about the late 1960s (Reiser 1992), a far more efficient system than the human mind and eye for the collation and analysis of complex numerical data and recognition of any deviation from the acceptable. Instant identification of potentially deleterious changes triggers alarms which alert the care-giver who then interprets and reacts to the situation. The carers are therefore no longer machine-minders as the machines mind themselves, but have become once again professional responders to patient-related events. Reiser argues that although machines remain central to the organisation of care, they simultaneously relieve the staff of the routine and precipitate behavioural responses only deliverable by the trained specialist professional.

The same process occurred after the introduction of large-scale dialysis: initially medical staff managed both machine and patient, as demand rose this was increasingly devolved to nurses and technicians with the doctors reserving the right to react to problems identified by other staff. From the days of the Copenhagen polio epidemic or the introduction of dialysis at Leeds, the delimiting factor for service provision was the availability of suitably competent personnel; this in turn was determined by training, finance and social forces. Expanding workload and the increasing sophistication and functions of commercial devices made intolerable the demands on staff. Again in nephrology, computer technology was incorporated by industry into dialysis machines, which became self-monitoring and self-regulating. Continuous interrogation by the machine, both of itself and of the patient, and alerts when events deviated outside the acceptable range (pre-set by the professional attenders) moved the machine from dependence on human control to autonomous self-governance. The corollary was that

[17] Blume thinks that 'instrument' is too simple a word for modern medical technologies, but it does convey the idea of a device used by and for the doctor. (Blume, S. (2000). Medicine, technology and industry. Companion to Medicine in the Twentieth Century
R. Cooter and J. V. Pickstone. London, Routledge**:** 171-185.)

the professionals were released from being mechanics to become supervisors of the patient-device interaction, dealing with complex situations only accessible to specialists.

The early dissonance between nephrology and intensive care and the later parallels were followed by a convergence particularly relevant to the present work. The most vulnerable and ill patients aggregate in the ICU, where medicine's "most sophisticated tools and efforts" (Peitzman 2007, p92) are directed towards the maintenance of life, for at least a while. It is precisely in these circumstances that ARF becomes the most frequent and severe organ failure, "a by-product of floridly expanding medical capability" (Peitzman 2007, p92). By the end of the 20th century 'critical care nephrology' (Ronco and Bellomo 1998) was essentially indistinguishable from other ICU activities, performed by intensivists. Renal failure in the ICU utilises different tools, different epidemiology and statistics, different approaches from those in 'mainstream' nephrology: in this respect the sub-specialty of nephrology came to have little commonality with its conceptual antecedent, general medicine.

1.5 Practice and Academia, Technology and Science.

1.5a Introduction

In the USA, there appear to be two categories of 'nephrologists': clinician-physiologists studying and treating renal disease within academic teaching centres; and those providing dialysis services for end-stage renal failure, predominantly in free-standing for-profit purpose-built facilities (Peitzman 1986; Peitzman 1989; Peitzman 1992; Peitzman 2001). In contrast, in the UK there is greater integration of renal services: the nephrologist not only investigates and treats fluid-electrolyte problems and glomerular disease, but also manages ESRD patients, their dialysis, their medical problems (both general and renal), and usually post-transplant follow-up. British nephrologists take an overt pride in providing a continuous 'cradle to grave' service for patients with kidney disorders as they progress, for example, from first presentation with the nephritic syndrome through progressive chronic renal failure to renal replacement therapy. British (and many European) renal physicians therefore claim to have integrated practice and academic medicine, technology and science. It is, however, arguable that this public stance is simply highlighting the positives of a situation determined by contingent circumstance: relatively few nephrologists *per capita*, concentration of resources within major centres, the NHS funding system, British referral patterns controlled by primary care physicians (GPs), absence of free-standing dialysis facilities independent of the local hospital centre, constrained academic budgets. The differences

in patterns of practice in the USA and UK appear historically to have been largely determined by the mechanism and extent of funding of both academic and clinical renal medicine. British nephrology merged the academic and the practical in the 1950s and 1960s, this transition perhaps being important in determining the initially fitful adoption of technology-driven practice.

The "ologies" claim an origin in investigational general medicine. Nephrologists like to think that their specialty started with the epochal clinicopathological correlates of Richard Bright in 1827 (Bright 1827; Bright 1836; Bright 1836; Osman 1937; Keith and Keys 1954; Bright 1983; Richet 1991). However, it was the laboratory-chemical approach of Golding Bird (1814 – 1854) and George Owen Rees (1813 – 1889) (working with Bright), developed in the 19th century European laboratory-medicine tradition (Foster 1959; Peitzman 1981; Coley 1986; Cameron 2002), and refined in the American metabolic-physiological laboratories of the 1930s and 1940s (Kohler 1979; Peitzman 1986; Peitzman 1988), which led to the recognition of renal disease as a distinct, complex, quantitative specialty. The study of glomerulonephritis ('Bright's disease') made little progress until the invention of the biopsy needle in the early 1950s allowed access to vital, as opposed to morbid, pathology. The clinicopathological contributions of Ellis and Addis in the 1940s (Ellis 1942; Peitzman 1988; Peitzman 1990), although almost instantly obsolete, restricted the conceptualisation of chronic renal disease for a decade or more (Peitzman 1992). There was, in this respect, a disjunction between the theory and the practice of nephrology at a critical time – the clinical practice was undergoing major change, whilst the pathological theory had to redefine itself after a century of stasis. Before the biopsy, academic nephrology received a further stimulus from the introduction of the flame photometer into clinical investigation, this device rapidly crossing into clinical practice because of its utility in the management of patients.

1.5b The science/practice debate

The relationship between laboratory-based medical science and clinical practice is not an easy one, with elements of mistrust and even contempt on both sides. The ambiguity of this relationship has been expressed by Berg (Berg 1995):

> "Medical care is only *aided* by science; it is not a science itself. The *practice* of medicine consists of *applying* scientific medical knowledge…" (p442)

> "The art of medicine to be successful requires a science to be applied. On the other hand, medical practice should never let this science impinge too closely - lest the artful ability to apply this science be lost." (pp 442-3)

Whilst this might be an ideal scenario (and Berg, a non-physician, is arguing for the application of scientific *method* to the practice of clinical medicine), the actuality is rather different.

The split between doctors and research physiologists is long-standing, and even discernible between Bernard or Virchow and their clinical contemporaries (Geison 1979)[18]. It would appear that whilst the ordinary practitioner may doubt the usefulness of much of the product of laboratories, the persistent conservative reaction to 'scientific' medicine may be more related to protecting their role, and hence their power-base, in the personal relationship with patients. This real or apparent conflict of perception between practice and science or personal care and technology lay at the heart of the resistance to specialisation within medicine in the first half of the 20th century (Lawrence 1985; Lawrence 1985; Lawrence 1999). Geison argues that although physiology is integral to medical education and was essential for the establishment of medicine as a learned scientific profession, it has increased the cost and duration of medical training without obvious (measurable) clinical benefits. The ordinary practitioner's scepticism of the value of 'scientific' medicine is based on deep-seated doubts as to the relevance of the products of the basic science to everyday health care[19]. Whilst practice may apply some segments of scientific output, for example in diagnosis, and use scientific language to establish professional credentials (Lawrence 1985; Lawrence 1997; Lawrence 1999), little basic scientific research impinges directly on practice. The 'esoteric knowledge base' has become too arcane even for the specialist practitioner. The science/practice dichotomy has been eloquently encapsulated by a distinguished academic clinical-scientist, Professor J Stewart Cameron, here writing as an historian of his specialty (Cameron and Hicks 1997):

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[18] Geison 1979, p71: "…persistent scepticism of many ordinary doctors toward experimental science from its beginnings to the present day."

Warner 1985, p45: "…the enduring ambivalence of many practicing physicians toward the laboratory's workers, methods, and products."

[19] "The increase of 'scientific paraphernalia' threatens to turn physicians into mindless technicians" Beecher H K. Clinical impression and clinical investigation. JAMA 1953; 151: 44-45.

"For the mechanization of an art, a skill or a culture cannot adequately take the place of the personal sensitivity of its followers, which had made a living thing of it, nor can the interpretation of a physical phenomenon replace the sympathetic understanding of a total human problem." Anon. Quality of medical care. NEJM 1952; 247: 34-35.

> "In many ways, technology defines organ-based specialties today, whilst research has moved in the opposite direction, so that basic work…is similar in the laboratories of all organ-based specialties; only the function of the whole organ remains unique to one area of study and, at the moment, is neglected in favour of more and more focussed dissection of cellular function. A new balance will need to be achieved…, by assembling these bricks again to make a house, so that we can understand what a home is." (pp 347-8).

It may, however, be that the anatomisation of modern medicine into laboratory science versus clinical practice has created a division more apparent than real. Whilst the practitioner might question the utility of the more arcane laboratory knowledge[20], and the academic challenge the generalizability of personalised empiricism, each 'side' has assimilated that which is cogent or applicable from the other. In all specialties, but particularly nephrology, physiological and pathological sciences are utilised in routine practice, perhaps subconsciously. Conversely, clinical problems, perhaps newly identified, have provided fertile territory for academic applied science rather than clinical pragmatic empiricism. The obverse of clinicians' suspicions of scientists is the latter's apparent disdain of the 'jobbing' practitioner or the 'tinkering' technologist. Much of the apparent conflict arises from the unequal balance of professional power, most evident in the USA, arising from and reinforced by the attitude towards, and funding of, research. Calvert suggests that the term 'basic science' is redolent with social contexts, being a socially constructed concept which enhances the status of scientists, although most of their activities are actually boundary work (Calvert 2006). Nevertheless, the American post-war ethos of 'scientific medicine' was central to the adoption of dialysis and development of nephrology as a specialty and therefore warrants further consideration.

The debate over the academic/practical divide in medicine has particular resonance in nephrology. Steven Peitzman, writing from an American perspective, is keenly aware of

[20] Lawrence 1985a, p505: "To defend the autonomy of clinical medicine, these physicians invoked an epistemology of individual experience which, by definition, defied analysis."
"…remarkable continuity in a rhetorical tradition in British medicine during years which saw profound changes in its organization, educational basis, and social relations...this clinical language was used to demonstrate the 'natural' qualities of leadership of hospital physicians and, therefore, to protect their interests against competition from scientifically minded practitioners and the pedagogical claims of a new generation of basic science teachers. To admit that clinical medicine could be made a science would be to dismantle a discipline and the patronage system on which it thrived."
Lawrence 1985b, p9: "yet another feature of this generalism in English medicine, and the valuation of a clinical art above a possible clinical science, was a disparagement of technology."

this and has argued its importance in the structuring of the specialty. John Harley Warner (Warner 1995), in reviewing the historiography, notes that "multiple sciences of medicine…coexisted at any historical moment" (p165) (to which one should perhaps add 'and at any geographical location'?). The many different threads of medical activity have been rephrased as ways of understanding (Toulmin 1976) or knowing (Pickstone 2000; Pickstone 2009). The relevance to nephrology of this continuing historically-grounded dialogue lies in its ability to inform the shaping of the specialty and the construction of the concept of ARF.

A thoughtful essay by Stephen Toulmin envisaged the spectrum of medical understandings as a matrix or grid, extremes on which might be portrayed as the 'pure' scientist and the general primary care practitioner. This portrayal may also be expressed as ways of knowing: analytical and scientific or holistic and personal. These extremes are often idealised abstractions, but nevertheless have been used as a framework on which analysis of specialty formation (or lack of it) has been built. Thus Christopher Lawrence's concept of 'incommunicable knowledge' (Lawrence 1985), that is to say the empirical art of medical practice based on experience, personal prestige, and collegiate status. Lawrence arraigns this abstract (London) physician against the medical science and technology emerging in the early 20th century and characterises it as a conflict between bedside and bench (Lawrence 1999), in which science, technology and specialisation struggled to gain a foothold in both pre-clinical curricula and in clinical practice. There is some time-limited support for Lawrence's thesis: for example, the introduction of the teaching of physiology at Oxford was delayed because of the attitudes of the medical elite (Romano 1997). Perhaps in contradiction, Butler suggests that British physiology in the same period became the elite influential science of intellectual skill in part because many of its leaders were as socially advantaged as their medical counterparts (Butler 1988). Balancing the art v. science argument are well researched instances of individuals and schools combining laboratory and clinical science to inform medical practice in, for example, France (Contrepois 2002) and Glasgow (Hull 2007).

It would therefore appear that even in the 19th and early 20th centuries there was a more marked tendency to assimilate scientific and technical knowledge into physicians' understandings than might have previously been suggested. Thus Pickstone's concepts of hybrid knowledge and teamwork in clinical research have a long lineage. Further, as the historical gaze is brought into closer focus it becomes apparent that, for the

specialties defined in the latter part of the 20th century, the distinction between clinicians and scientists has blurred into indiscernibility. The traditional view of confrontation between clinical and scientific thought has been vigorously challenged by Sturdy, who suggests that this was a socially teleological view based on the assumption that professions act to obtain and consolidate power (Sturdy 2011). As we have illustrated, this sociological view ignores cooperative endeavours and the reciprocal connections (Sturdy 2007) within the matrix of activities in the clinic and the laboratory, however defined.

Toulmin encompassed the multifarious expressions of physicians' understandings by applying Susan Leigh Star's useful concept of triangulation (Star 1989) to the reticulation of medical knowledge and practice. By so doing, science and practice combine in varying proportions for individual practitioners or specialists. So, for example, the multifaceted construction of a modern specialty can be illustrated by reference to radiotherapy, another technology-orientated specialty which crosses traditional medicine/surgery and science/practice boundaries. Hayter has shown that the new knowledge came equally from the clinic and the laboratory and that radiotherapy entered medicine "through a portal of empiricism" (Hayter 1998). As with clinical nephrology, radiotherapy was only adopted by the laboratory after a "preparatory phase of enthusiastic empiricism". The physical properties of dialysis and the biological basis of renal disease were largely elucidated after treatment had been tried, but the incorporation of applied science permitted its safe and rational use in patients. Similarly, Hayter contends that radiotherapy "as it emerged at the end of the 20th century is…a synthesis of many decades of clinical observation and basic science investigation. Its history demonstrates that neither the clinic nor the laboratory can claim complete authority over the practice of [specialist] medicine."

1.5c Academic inheritance of nephrology

Physiological studies of the kidney grew in France and at Guy's Hospital, London in the early 19th century as a chemical dissection of the metabolic consequences of renal failure. These investigations by medical chemists had no contemporary therapeutic corollary but had consequences a century later. The biochemical understanding of uraemia underpinned the efforts of those developing dialysis. However, as will be discussed in the relevant chapter, uraemia was seen as a clinical, not a scientific, problem seeking a technical solution. The clinical science of renal failure blossomed only after the empirical technology had been established, releasing a substantial

surviving clinical study-base. The continuation of physiological research largely divorced from clinical practice did, however, nurture a fundamental divide in many of the specialties newly arising after the war. The continuing American fascination with science, encouraged by generous funding, greatly increased the numbers and enhanced the status of academic renal scientists, as Peitzman has repeatedly argued. This established bloc often appeared at odds with the technology-based practitioners seeking to establish themselves under the same specialty umbrella (Peitzman 1986; Peitzman 1996; Peitzman 1997; Peitzman 2001).

By the mid-1940s the nascent specialty of nephrology provided a paradigm for academic medicine as envisaged in the German schools, developed by the Osler-Flexner model of medical education in the USA and enhanced by a funding system which was later perpetuated by the powerful contributions to basic science by the NIH and Veterans Administration (and, to a much lesser extent, the MRC and NKRF in the UK). The paradigm was (is) an intellectual elite in 'centres of excellence' conducting minutely elegant quantitative studies on a numerically restricted group of patients, who were untreatable other than by 'regimen' based on these studies. It is relevant that of the so-called 'greats' of (American) nephrology in the middle of the 20th century, only 2 of 7 were practicing physicians (Peitzman 1988); likewise, of the 27 present at the inaugural meeting of the UK Renal Association in 1950, only 3 were physicians (Cameron 2000). That nephrology was predominantly scientific, rather than clinically pragmatic, was to have repercussions when it was confronted by the rude mechanics of the "therapeutic revolution" of the late 1940s. Similarly, cardiology until the mid-20th century was an esoteric academic discipline based on physiological studies such as by Starling and Dale – a basis for academic empires, not therapy. Admittedly, cardiology had digitalis and one or two other drugs, but these were in the province of the general physician and were not products of the intellectual specialty base of the time. The ECG machine, although developed early in the 20th century, was little used and did not influence treatment. Indeed, Lewis, who had pioneered its use, found it of no utility when presented with a specific clinical problem and abandoned his interest in the machine and in cardiology. Although it had been shown in 1918 that the ECG could be used to precisely diagnose myocardial infarction, the condition only became clinically "acceptable" in the 1930s (Howell 1984; Howell 1988).

For the first half of the 20th century, academic study of kidney disorders was centred almost exclusively in a small number of the medical schools and universities of the USA

(Peitzman 1986; Peitzman 1988; Peitzman 1990; Peitzman 1996). Scientific (or laboratory) medicine, based on the teaching of and research in physiology, had become the foundation of the American medical curriculum (Perkins 1997); reinforced by the funding of basic medical research by university foundations and charities such as the Rockefeller Foundation (Starr 1982)[21]. There was less institutional, charitable, or governmental financial support for the practice of medicine or the application of technology. From the 1920s and 1930s, the Rockefeller Institute (together with the MRC and the Nuffield Foundation) also supported reformation of medical education in the UK along the same pattern of applied science founded on research. Progress was slow in England, particularly London, starting with Thomas Lewis' medical research department at University College Hospital, where a full-time professor of medicine was appointed in 1929 (Fisher 1987). But English medical schools did not become fully university-based until after the Goodenough Report in 1944 (Graham 1970).

1.5d Post-war biomedicine in the USA

Most commentators appear to agree that World War II resulted in a sea-change in the attitudes and aspirations of American medicine. There is historical consensus that the public acceptance of the beneficial centrality of scientific progress generated huge government investment in science, that this attitude and its financial corollary fed off each other in a reciprocating fashion, and that the existing professional structures (universities and their hospitals, and academic departments of medicine) gained the most from the new situation. Starr, in his detailed social economic analysis of American health care, says of the prevailing post-war attitude:

> "Americans now gave science unprecedented recognition as a national asset. During World War II the research effort…persuaded even the sceptical that support of science was vital to national security." (Starr 1982, p335).

The establishment in 1941 of the Office of Scientific Research and Development (which had two parallel committees: one for defence and the other [Committee on Medical Research, CMR] for medicine) was the key wartime development which freed up federal investment in research. A feature of this government funding of research – outweighing in significance the huge injection of resources – was that the government contracted, in the form of grants, with autonomous institutions. The CMR distributed

[21] Between 1902 and 1938, the Rockefeller Institute for Medical Research, New York, received $65million from John D Rockefeller, so that its budget greatly overshadowed federal expenditure on health. In 1938, the Public Health Service (incorporating the National Institute for Health) budget was $2.8million, whilst that for research in the Department of Agriculture was $26.3million. (Starr 1982, p339).

$15million in the form of 450 contracts with universities and 150 with research institutes and hospitals[22]. Not only did World War II, "more than the New Deal, mark the beginning of the great expansion of the federal government's support of medicine" but it also set the long-term pattern for funding of medical research: investment without control.

James Shannon, Director of the NIH and sometime renal physiologist, as part of a 20-year review of its performance (Shannon 1967) considered the founding contexts (strictly, the post-war re-founding). He emphasised the shift in Federal concern toward active intervention for the population during the 1930s, as shown by the New Deal and the National Cancer Act (1937). The scientifically fruitful wartime partnership between the state and the universities set a pattern that was formalised by the Public Health Service Act of 1944, in which Title III authorised the Surgeon General to foster and support research in health and disease. The optimistic post-war culture (in the USA, if not in the UK) led to high expectations of the promise of science. Hence policy-makers were favourably disposed to provide generous support, achievable because of the booming economy. Shannon made a further point, not greatly developed by later commentators, that the voluntary philanthropic agencies had had their activities curtailed by the Depression and the war. At the end of the war, the magnitude of the challenge facing the biomedical sciences was perceived to be too great to be met by the voluntary approach alone. However, the Federal authorities adopted a central tenet from the voluntary sector. Citing the success of the National Foundation for Infantile Paralysis in identifying single issues of public need, the NIH developed its 'categorical concept' of single disease programmes, which remained policy and resulted in the multiplication of organ- or disease-specific divisions.

Federal expenditure on medical research grew exponentially (Endicott and Allen 1953), the trajectory of increase far outstripping the rate of rise in the total national income, (Starr 1982, p342):

[22] Starr p341: "Most of the work took advantage of the tremendous backlog of scientific ideas awaiting application. It was carried out primarily in independent laboratories. Scientific decisions were left to panels of independent scientists, and there was little governmental control of scientific work after grants were awarded. This was the pattern even in the OSRD's military research, and it was widely considered not merely a success, but a lesson for the future that was pregnant with political meaning." "The Allied victories in scientific work seemed to testify for a political system that gave science as well as its citizens more autonomy. This experience strengthened the case of American scientists, universities, and the medical profession that the research sponsored by the government ought to be performed under minimal control primarily in independent institutions, rather than in government laboratory as was generally the practice in Europe. Here was yet another point of structural choice, when American institutions moved toward greater private control and functional autonomy than has been the European pattern."

Table 1.1 NIH Budget ($million)

1945	1947	1950	1955	1960
0.18	4	46.3	81	400

Nevertheless, the NIH remained the only federal agency in which officials could not allocate money without the approval of part-time committees representing the beneficiaries and, further, had no control over the research programmes once the funds had been allocated. The Medical Director[23] of the US Public Health Service, writing in 1946 in a leading American journal (van Slyke 1946) to reassure and encourage the scientific community, stated that from its inception the NIH extramural grants were to be "a medical research program of scientists by scientists". The underlying philosophy was "the integrity and independence of the research worker and his freedom from control, direction, regimentation, and outside interference". This attitude meshed exactly with the entrenched American distrust of governmental control, what they believe to be "socialism", and fears of the "institutionalisation" of research. It also effectively depoliticised support for scientific endeavour [24]."To a remarkable degree, control over research was ceded to the scientific community. The approval of grant applications as well as basic policy issues rested with panels of nongovernmental scientists. The individual scientist, too, enjoyed autonomy within the constraints of professional competition." (Starr 1982, p343). Starr considers that this reflected the prevailing public ethos about science: "This grant of autonomy expressed, in a concrete way, the public trust in science and governmental acceptance of scientists' demand that they be left to follow their own rules." (p344). Independence from state control remained an untouchable US policy[25].

Coincident with the huge injection of government resources into medicine, the 1940s saw the emergence of a powerful, private, lay lobby for medical research which reflected the new status of research as a popular cause. "Public opinion confirmed the breadth of

[23] Also an academic renal physiologist.

[24] 20 years later, the then Director reiterated this ethos (Shannon 1967, pp104-5): "In the absence of a broad general theory, such as exists in the physical sciences, the development of diagnostic, therapeutic, and preventive capability will continue to be dependent upon empirical approaches, serendipity, and the intuitive brilliance of too few gifted individuals. Therefore, the hope of major advances lies in sustaining broad and free-ranging inquiry into all aspects of the phenomena of life, limited only by the criteria of excellence, the scientific importance, and the seriousness and competence of the investigator."

[25] In 1951, officials of the NIH Division of Research Grants outlined the government's stance: "The investigator works on problems of his own choosing and is not obliged to adhere to a preconceived plan. He is free to publish as he sees fit and to change his research without clearance if he finds new and more promising leads. He has almost complete budget freedom as long as he uses the funds for research purposes and expends them in accordance with local institutional rules." (Endicott K M and Allen E M. 1953).

this sentiment, and politicians were not insensible to the possibilities." (Starr 1982, p343). Medical research became deeply politicised, not so much because it was a good 'vote winner' but because it became emblematic of, and a diversionary tactic within, the political belief struggle within the nation and within the medical profession between liberal and reactionary, reformers and conservative, social and private[26]. Significantly, the differences between reforming liberals and the influential American Medical Association could be sublimated in cooperative promotion of investment in medical science and facilities. The NIH and the voluntary organisations discovered that "the way to open wide the public's purse was to call attention to one disease at a time" (p343) (the 'categorical approach'). A tangible result was the formation of the National Heart Institute (which also covered renal) in 1948, shortly followed by five others (all within the ambit of the National Institute(s) of Health). The freedom enjoyed by the medical profession is exemplified by the decision by Congress to empower the Surgeon General to set up such research institutes as he saw fit (the "Omnibus Act" of 1950). The governmental largesse was such that "medical researchers went direct to Congress…to take advantage of the distinctive good will medicine enjoyed" (Starr 1982, p343). The sum of this was a huge increase in medical research expenditure from the 1940s onwards:

	1941	1946	1951	1966
Federal	$3 million	$28 million	$76 million	$1.4 billion
NIH		$8.3 million		$800 million
Total	$18 million	$87 million	$181 million	$2.25 billion

Table 1.2 Medical Research Expenditure (excluding construction and training)

(Modified from Shannon (1967) and Starr (1982))

The dramatic Federal intervention in research in biomedical sciences can be illustrated by the number and value of specific grants given by government in general (Deignan and Miller 1952) and the NIH in particular (Endicott and Allen 1953) in the immediate post-war era. The marked increase in funding from private sources should also be noted and is perhaps an even more sensitive barometer of the increasing affluence of American society at a time when other countries were struggling economically.

[26] "Opponents of national health insurance could display their deep concern for health by voting generous appropriations for medical research" (Starr 1982, p343)

Research into kidney diseases disproportionately benefitted from this injection of riches (Deignan and Miller 1952), being the third highest recipient of grant monies in 1946 – 1951 after poliomyelitis (entirely private funding) and 'arteriosclerosis and hypertension' (which would also include renal-related research). Government funding of kidney research increased from nothing in 1946 to $1.3million in 1951. These grants went to established academic centres and were almost exclusively for 'basic' physiological research (see Table1.3).

	1945	1946	1947	1948	1949	1950	1951	1952	1953
Government		$1,871,065*	$5,807,147	$12,859,975	$19,466,388	$21,320,493	$21,785,603*		
NIH	$85,030**	$780,158	$3,437,280	$8,874,463	$10,871,492	$12,984,000	$16,374,128	$18,408,000	$20,468,000
Private		$2,436,376*	$4,447,193	$8,597,772	$13,663,730	$11,680,377	$11,108,006*		
Kidney Diseases									
Government		---	$227,150	$418,745	$648,052	$873,226	$1,309,151		
Private		$53,090	$111,700	$105,682	$177,818	$186,703	$209,924		

Table 1.3 Grants for medical research and into kidney diseases.

(Modified from Deignan and Miller 1952, Endicott and Allen 1953)

* Data for 1946 and 1951 incomplete. ** For cancer alone.

In the first 20 years of the reformed NIH, the Federal contribution increased 50-fold, and rose from 31% to 68% of the total medical research expenditure, the NIH portion rising 24-fold (15x, corrected for inflation). Between 1930 and 1945 most of the very much smaller NIH budget had been devoted to intramural research at Bethesda, thereafter it went national[27]. Apparently as deliberate policy, government grants were rolled out across the nation so that, although New York consistently received the largest percentage of grant monies, academic centres nationwide benefitted from the new largesse (Deignan and Miller 1952). Non-governmental research grants (from foundations, etc.) followed a similar pattern. It might be inferred that medical research was benefitted twice over: not only did academic centres receive hugely increased monies, but also the distribution of and amount of private funding was influenced by Federal policy.

Undoubtedly, a key factor in determining this abundance was the post-war American prosperity[28] which starkly contrasted with the economic situation in Britain and Europe (Davies 1996; Charmley 2001). A clear beneficiary of the massive investment in and goodwill towards medical research was the nascent specialty of nephrology [29]. Prior to the 1940s, renal disease was regarded as an uncommon and intractable clinical problem. On the other hand, kidney function in health and disease was an ideal subject for physiological research (Peitzman 1986; Peitzman 1988; Peitzman 1989). Consequently, renal medicine was confined to university academic departments, many led by non-clinicians. The revolution in the quantity and quality of research funding was channelled through, and controlled by, such university departments of medicine. The balance in medical schools between clinical and basic science was radically altered by the growth in research funds, so that science and clinical departments were no longer functionally

[27] "Never in the nation's history had public funds in such amounts been placed at the disposal of individuals working in support of their own objectives outside the framework of federal institutions." (Shannon 1967, p103)

[28] Starr 1982, p336: "Postwar recognition of a national interest in science and medicine also stemmed from America's new role of international leadership. European economies were devastated while American industrial production and national income more than doubled during the war. And in the Cold War, science assumed a symbolic as well as a practical function in maintaining America's position as 'leader of the free world'." "Prosperity gave the Americans the opportunity to worry about their health, and it also changed the health problems they worried about."

[29] Weisz 2006, p193: "Different specialties…had unequal access to elite institutions…Within this elite sphere it often did not matter whether a particular kind of problem was widespread or not. There might be a niche for small numbers of high-level specialists devoting themselves to relatively rare problems. Those fields that became subspecialties of internal medicine…- gastroenterology, nephrology, cardiology – are particularly good examples of this sort of development."

interrelated because of the emphasis on basic science rather than clinical science. "The separation between medical *practice* and *science* is pervasive in the early post-war years" (Berg 1995, p441) and, at least for nephrology, has persisted ever since (Peitzman 1986; Peitzman 1988; Peitzman 1989; Peitzman 1992). As Stephen Kunitz has noted (Kunitz 1988), the post-war Federal largesse hugely increased the number of investigators, but most studied "nonhuman, nondisease" topics. Physicians competed, with mixed success, with scientists in laboratory work which was mainly directed towards aetiology and pathogenesis and consequently forsook the bedside where their expertise (in prognosis and therapy) could have been better applied. However, from the 1970s NIH funding remained more or less constant but resources for clinical care, in particular from Medicare, increased. This tended to redress the balance as entry into investigational careers became more stringent, resulting in a two-track promotional system.

Post-war American government expenditure on health care was not limited to financing research but was also directed towards hospital construction and the structure of the medical profession. The changes may be summarised thus (based on Starr 1982, p335):

	1950	1960
Medical Workforce	1.2 million	3.9 million
Health Care Expenditure (all sources)	$12.7 billion	$71.6 billion
Per cent Gross National Product	4.5%	7.3%

Table 1.4 US Health Care Expenditure

The university hospitals further benefitted from the Health Research Facilities Construction Act and the introduction of NIH fellowships, both in 1956, which gave academic centres yet more resources over and above the programme grants. Taking an historical perspective, Starr opined (p338):

> "Aiding medical research and facilities construction…set off an unbalanced expansion that became increasingly costly and irrational…favoring growth without redistribution…"

Hospital construction programmes were adopted immediately after the war "almost without dissent". The law enabling hospital development[30] (known as the Hill-Burton programme, but actually redrafted by Taft) carefully limited political, especially federal,

[30] The Hospital Survey and Construction Act, 1946.

discretion (Starr 1982, p349) and also restricted the hospital building programme to 4.5 beds/1000 population (well above the levels obtaining in any State). Far from being a ceiling on development, this number rapidly became a *target*. Between 1947 and 1971, $3.7 billion of federal money was allocated for hospital construction which generated $9.1 billion in local and state matching funds (Starr 1982, p350). This injection of resources resulted in unregulated expansion of the hospital service. "In effect, by earmarking money for specific purposes and then outlawing federal interference, Congress and the professions joined in restricting any tendency toward administrative rationalization." (Starr 1982, p351).

The consequences were twofold. The "universities became the umbrella organizations for America's regional medical centers, which instead of being organized around the immediate needs of patients, were oriented primarily toward research and training." (Starr 1982, p361) Simultaneously, through NIH (Turner 1967) and other research funding, there was a massive increase in medical school income (but not in numbers of students) (Starr 1982, p352). As a direct consequence, there was an even greater increase in staffing levels of medical faculties, which increased by 51% during the 1940s and by 270% in the 1950s. The disconnect between the research and the educational functions of universities was gradually realised by the Federal paymasters (Shannon 1967; Turner 1967). The attempt to redress the balance (Health Professionals Assistance Act 1963) initially only funded new facilities, thereby further entrenching the power of the institutions without increasing the production of medical students. Some of the medical manpower shortfall was filled by considerable medical immigration, but it seems reasonable to infer that the medical establishment was not whole-heartedly committed to expansion of the potentially competing workforce. Shannon (1967, p102) expressed the tensions between the state and the universities, and within and between research and educational activities, thus: "persistent ambivalence concerning the extent to which research is an academic function supported by public funds, or a public function housed in universities." The increase in size of the departments of medicine encouraged fragmentation into subspecialties, which themselves generated an increased demand for academic physicians. "The economic rewards to specialization were considerable." (Starr 1982, p356).

The second consequence was that the investment in Veterans Administration and community hospitals was accompanied by strong incentives to provide specialist postgraduate medical training, for which they necessarily had to become affiliated to the

Table 1.5 Average Medical School Income

1940s	$500,000 rising to $1.5 million/year
1959	$3.7 million
1969	$15 million

university hospitals. Thus, the Veterans Administration not only paid its hospitals to provide postgraduate training but also would only recognise Board-certified specialists as eligible for staff appointments. There was thus a self-perpetuating system, fuelled by a massive influx of public and private resources, of a rapid hospitalisation of American medicine, a system wherein the specialist was the key player (Starr 1982; Stevens 1988; Stevens 1989; Stevens 1998). The number of residency positions and full-time hospital specialists increased dramatically (Starr 1982, pp358-9):

	1940	1947	1955
Residency positions	5000	>12000	25000
% Full-time specialists	24%	37%	44%
			(1966 = 69%)

The overall picture was reflected in internal medicine (Stevens 1988, p352):

	1940	1950	1960
Residency positions	~700	>3700	5500
Board-certified	2158		11155

It is obvious that the emerging specialties took full advantage of this fruitful situation (Starr 1982; Stevens 1989; Stevens 1998; Leeming 2001; Weisz 2006). However, as previously indicated, the relationship between research, hospital and university funding was an iterative self-sustaining process, an indication of which is neatly summarised by Starr (p358): "As the medical schools replaced part-time instructors from private practice with full-time professors from research backgrounds, they were also substituting new models of professional competence."

The pattern of American practice was set in the immediate post-war period in response to a public perception of the value of science in general and medical science in particular, in a period of affluence and optimism, and was established by an alliance of politicians and professionals, both groups benefiting from its perpetuation. The flowering of technology-based medicine (and its subservient specialties) could be represented as a 'peace dividend' enabled by freeing resources from the military to be applied to civilian welfare. It could be argued that the investment was a continuation of the attitudes and wealth fostered in America by war, and the national pride in scientific

achievement an extension of national power. In contrast, the European and Asian post-bellum legacy was austerity, reconstruction and social realignment; circumstances not conducive to medical or scientific largesse (Hennessy 1992; Kynaston 2007). The unsystematic US health care system was a fertile seed-bed for the development of specialties, particularly those such as nephrology which were overtly scientific, technological, and restricted to hospital practice. As will be explored later, this scenario was in complete contrast to that obtaining in Britain, where the specialty of nephrology and its identifying technology of dialysis struggled to be accepted and established.

TABLE 1.6. EARLY NEPHROLOGY SOCIETIES
(Modified from Cameron 2002, p180)

Date	Society	Scope
1949	Societe de Pathologie Renale (Societe de Nephrologie from 1959)	Francophone countries
1950	Renal Association	UK
1950	National Nephrosis Foundation (one of the forerunners of the National Kidney Foundation from 1961)	USA
1955	American Society for Artificial Internal Organs	USA & Canada
1957	Societa Italiana di Nefrologia	Italy
1960	International Society of Nephrology	Worldwide
1960	Sociedad Argentina de Nefrologia	Argentina
1960	Sociedad Brasilero de Nefrologia	Brazil
1961	Gesellschaft fur Nephrologie	German-speaking countries
1964	European Dialysis and Transplant Association (from 1984 EDTA-ERA)	Europe
1964	Sociedad Espanola de Nefrologia	Spain
1966	American Society of Nephrology	USA (worldwide)

TABLE 1.7 EARLY JOURNALS DEVOTED TO NEPHROLOGY

Date	Journal	Language	Country
1954	Minerva Nefrologica	Italian	Italy
1955	Transactions of ASAIO (ASAIO Journal from 1988)	English	USA
1963	Nephron *	English/French	Switzerland
1963	Actualities Nephrologiques de L'Hopital Necker *	French (English from 1969)	France
1964	Proceedings of EDTA (Nephrology Dialysis Transplantation from 1984)	English	UK (European)
1965	Contributions to Nephrology *	English	Switzerland
1971	Nieren- und Hochdruckkrenkheiten *	German	Germany
1971	Kidney International	English/French	Germany
1973	Clinical Nephrology *	English	Germany
1976	Dialysis Transplantation *	English	USA
1976	Artificial Organs	English	USA
1977	International Journal of Artificial Internal Organs	English	USA
1977	Journal of Dialysis	English	USA
1980	American Journal of Nephrology *	English	USA
1980	Seminars in Nephrology *	English	USA
1981	Peritoneal Dialysis Bulletin (Peritoneal Dialysis International from 1988)	English	Canada
1982	American Journal of Kidney Diseases *	English	USA
1982	Blood Purification	English	USA
1986	Pediatric Nephrology	English	USA
1988	Journal of Nephrology	English	Australia
1989	Journal of the American Society of Nephrology	English	USA
1986	Seminars in Dialysis *	English	USA
1994	Nephrology	English	USA
1995	Experimental Nephrology *	English	USA
1996	Home Hemodialysis International	English	USA

- All bilingual journals became monolingual English publications.
- * Published independently of specialist societies
- Not all publications still in existence

2. **DIALYSIS – INVENTION, DIFFUSION, RESISTANCE.**

"In medicine a new therapy begins as an unusual, perhaps dramatic, but certainly out of the ordinary event." (Koenig 1988, p469).

"History can help identify what past choices have been made and what the effects of those choices have been, or, perhaps most important, to identify that there were in fact choices to be made." (Howell 1995, p229).

2.1 Introduction

The pattern of uptake of a medical innovation is conventionally described as a sigmoid curve (Banta 1984): a slow initial phase in which the inventor and enthusiastic patrons attempt to persuade others of its utility; a phase of rapid acceptance wherein individuals and organisations feel compelled to adopt the novelty (which may not be in its original form but may have been 'refined'); and a final period in which uptake flattens as the market becomes saturated. This life-cycle does not accommodate those innovations which either disappear (perhaps to later reappear in a different configuration) before completing the initial phase, or fade away after general acceptance because their use does not fit with changing practice or they are superseded by other developments. A further exception to the sigmoid-curve pattern is Warner's 'desperation-reaction model' (Warner 1975) in which an innovation is very rapidly, and perhaps uncritically, taken up because it is perceived to fill a therapeutic void: Warner cites the introduction of chemotherapy for leukaemia as an exemplar. This rapid linear trajectory is exceptional except possibly for some pharmaceuticals. The post-war introduction of dialysis most closely followed the sigmoid pattern, although Peitzman argues that the justification for some aspects of its later uptake rather mimics the desperation-reaction model.

In this chapter the first, rather slow phase of the diffusion of dialysis will be considered. This phase has been frequently categorised as 'resistance' to innovation, an analysis couched in terms of a power struggle between older established practitioners and a new breed of younger entrepreneurial enthusiasts who challenged the status of the empowered establishment. This socially teleological analysis simplifies the typical situation: the rate at which an innovation receives general approval is more usually controlled by multiple social and practical factors. Most, if not all, new inventions come into view not as the finished article but with more prototypical characteristics: they may appear to the objective observer as clumsy, difficult to use or even potentially dangerous.

Health care institutions do not have limitless reserves of uncommitted finance, so require convincing by evidence or persuasion to invest in new treatments. Technologies invariably come to the medical marketplace without a body of statistical evidence to prove their worth: unlike pharmaceuticals, machines and procedures are rarely if ever scrutinised by randomised clinical trials or other objective evaluation before or after general adoption. The absence of statistical objectification for a particular deviation from accepted practice compounds the difficulty presented by the simultaneous appearance of competing technologies: the audience is being asked to both accept new concepts and to choose between candidates. Innovations may seek to address problems generally considered to be either unimportant or, more likely, to be perfectly well treated by practices based on the prevalent theories (Pickstone 1992). These difficulties facing innovations are more likely to be perceived by experienced (i.e. older) practitioners, who may feel obliged to counsel caution and to advocate established alternatives. This attitude could be construed as responsible caution or reactionary conservatism and was a particular issue in the establishment of dialysis and nephrology.

The history of the invention and adoption of dialysis has been variously treated: as a sequential history (Drukker 1989; Drukker 1989; Gottschalk and Fellner 1997), a record of people and events with analysis (Cameron 2002), as personal memoir (Alwall 1986; Scribner 1990; Schreiner 1999; van Noordwijk 2001), or as popular biography (Heiney 2002). The literature has not necessarily contextualised this innovation in terms of social historical analysis, except in the body of work on American nephrology by Peitzman. This chapter will attempt to situate the history of dialysis in terms of the concepts of the social history of technology, to test its fit, and set the scene for events in Britain. The focus is necessarily on the haemodialysis machine (often called the artificial kidney in the early days) as this was the iconic device which defined the specialty of nephrology. There were, however, competing technologies and so the choices between treatment modalities also receives attention.

Events, people and places in the story of dialysis have been well documented and are summarised in Tables 2.1 and 2.2 (Drukker 1989; Drukker 1989; Cameron 2002). The key moment is taken to be the invention of a clinically usable dialysis machine by Willem Johan (‘Pim’) Kolff (1911 - 2009) in 1943 in occupied Holland, an event which has assumed almost mythical proportions (Heiney 2002): portrayed as the struggle of one man in appalling circumstances, whilst continuing to practice medicine, supporting

the resistance movement, and raising a family. This reading of the history of the invention of dialysis has been succinctly summarised by Cameron (2002, p90):

"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…postponed Alwall and Murray's application of the treatment to humans by several years.[31] Thus unlike Kolff's long period of trial and error before successful dialysis could be reported, both Murray and Alwall independently were able to report successful dialyses almost immediately they moved into the clinical field."

Figure 2.1 Replica Kolff Rotating Drum Dialysis Machine, c1943.

[31] "…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 was dependent on the permission of the director of our medical department, who feared the new method. The general opinion was adverse." (Alwall 1986, p87).

Figure 2.2 Replica Abel-Turner-Rowntree Vividiffusion Device, c1916

Figure 2.3 Walter Elliott assembling Alwall Machine, Newcastle c 1958

Figure 2.4. Modern Dialysis Monitor, c2005.

2.2 What is haemodialysis?

A modern dialysis system consists of several components:

- the dialyser: a semipermeable membrane of known performance which is spun as a hollow capillary with microscopic internal diameter, thousands of these being bundled together in a sterilisable format, separating the patient's blood from the 'cleansing' fluid of known composition – the dialysate;
- a pump and tubing continuously circulating blood from the patient through the dialyser;
- a needle or other vascular access to attach the system to the patient's circulation;
- a pump for controlled delivery of anticoagulant (almost invariably heparin) to prevent clotting of blood in the circuit;
- a pump to mix ultrapure water in high volume (600 mls/min) with concentrated and buffered dialysate;
- a host of computerised safety devices which monitor and control the function of the system.

The sophisticated modern commercial machine is virtually self-sufficient, the product of 50 years' refinement, and requires little human control after the desired parameters have been set. It differs little in principle from the devices of the 1940s, only in the incorporation of systems which control quality and ensure patient safety. Of course, the packaging of the machines makes them appear far different from the crude devices assembled from available bits and pieces by Kolff and others.

Figure 2.5. Modern Capillary Fibre Dialysers

Of the components of the dialysis system, those critical to its invention were the membrane and the anticoagulant. There are a number of natural and semi-natural membranes that are semipermeable (that is, allow the diffusion of water and solutes of

particular molecular size) and the availability of commercial cellophane tubing from 1929 (sausage skin) provided a readily available, manageable product which had the performance characteristics suitable for dialysis[32] (Figure 2.6). The other development that allowed clinical dialysis was the discovery and purification of heparin[33] (Figure 2.7). Its predecessor, hirudin was an adequate anticoagulant but its purification from leeches resulted in contamination so that in clinical use it frequently, if not invariably, caused severe toxic reactions. Heparin was also derived from animal tissue but could be purified and was more predictable in clinical use. As Cameron (2002, p68) succinctly puts it:

> "…with heparin available, the remaining great technical problem of a suitable, really robust dialysis membrane, easily sterilised without damage to the material or alteration in its properties and with a long shelf-life…was solved, outside medicine or even science, by the packaging industry."

1839	'Cellulose' named by Academie des Sciences
1885	Cellulose purified from wood by Charles Cross & Edward Bevan, Royal Botanic Gardens, Kew
1908	Joseph Brandenburger regenerated cellulose acetate in sheet form
1910	"Cellophane" available from Societe Industrielle de Thaon
1927	Freda Wilson, Vancouver, showed it could be easily sterilised
1920s	Visking Co, Chicago: sausage skin
1928	FC Andrus use of sausage skin for ultrafiltration

References:

Wilson FL. Experiment with cellophane as a sterilisable dialyzable membrane. Arch Pathol Lab Med 1927; 127: 239

Andrus FC. Use of Visking sausage casing for ultrafiltration. Proc Soc Exp Biol Med 1929; 27: 127 - 128

Figure 2.6. Chronology of cellulose

Perhaps Cameron is correct in stating that, with the various components available, the invention of the dialysis machine was inevitable[34]. However, it required an informed,

[32] Cameron 2002, p188: "Indeed it can be said that the search for better electrical insulation [PVC and PTFE, adapted for blood tubing], together with sausage manufacture has done more for patients in renal failure than all the purely medical research invested in the subject."

[33] Cameron 2002, p63: Heparin "…despite increasing competition, remains the standard anticoagulant for haemodialysis…Heparin has played such a major role in both the introduction and the success of haemodialysis that dialysis almost becomes unthinkable without it." See also George (1998) and Marcum (2000).

[34] Kolff later rather disingenuously stated: "Since I had both heparin and cellophane, all that remained was to build a dialyzer of sufficient capacity to make application clinically worthwhile."

imaginative[35], inventive mind to solve a practical problem – an intellectual achievement transcending mere empirical tinkering.

1821	JL Prevost, JB Dumas defibrinated blood by whisking
1849	CE Loebell perfused organs with defibrinated blood
1862	E Bidder "
1876	G Bunge, O Schmeiderberg perfused kidneys with oxygenated blood
1884	John B Haycroft (Birmingham, UK) anticoagulant extract from heads of leeches
1903	Friedrich Franz moderately pure hirudin
1904	C Jacoby named 'hirudin' – used in organ perfusion experiments (but, impurities → frequent toxic reactions) E Sachs & Co (Leipzig) commercial hirudin
1916	Jay Maclean (1890-1957) extracted heparin ("heparphosphatid") from liver (medical student at Johns Hopkins Hospital)
1918	William Henry Howell (1860-1945) prepared and named 'heparin' (Maclean's boss)
1923	Crude extract heparin available
1924	Heparin used in blood transfusion
1926	Heinrich Necheles (1897-1979) Heparin in experimental dialysis (Peking)
1930s	Charles Best (1899-1978), Gordon Murray (1894-1976) and others used purified heparin for thrombotic conditions (Toronto)

Figure 2.7. Chronology of anticoagulation

2.3 Background to invention

Although Cameron considers that it was 'inevitable' that a dialysis machine would have been invented in the 1940s, the available evidence does not necessarily support either this deterministic viewpoint or adequately explain the remarkable concurrence of its invention by three truly independent individuals, each of whom, because of the war, were totally unaware of the others' work. Interestingly, none of the inventors refer to the earliest clinical dialyses performed by Georg Haas (1886 – 1971) (Wizemann and Benedum 1994; Wizemann and Ritz 1998) in the 1920s, who not only performed dialysis but also observed a number of the key clinical features of the procedure. Presumably he abandoned further attempts because it proved ineffectual (predictably so because the patients had chronic renal failure and the dialyses were inadequate to confer any significant clinical or biochemical benefit - the duration was too short, the method

[35] Kolff used the water pump from a Ford model T engine to provide the rotational coupling connecting the blood tubing to the rotating drum of the dialyser, and metal from a shot-down bomber and, when the metal ran out, wood.

was fractionated rather than continuous blood flow, the membrane surface area was too small)[36].

Multiple independent invention is not infrequent and may be ascribed to a common knowledge base and similar competitive situations (Westrum 1991), although the products of invention may vary in detail because of the inventors' different orientations and resources. Concurrence suggests that an unfulfilled need is apparent and some set of conditions has appeared to meet this need (Hindle 1983). Westrum's view is:

> "Thus, very little that is invented is completely new. Even the basic idea for the invention has been 'in the air' for a considerable time…The components of the invention have frequently been available for some time. And the inventor seldom works alone, but is assisted by others who get relatively little credit in the history books, even though their ideas are often important. Others may be working on the same innovation but have chosen a less fruitful or more difficult path; they rarely get credit in the history books either. The inventions themselves arise in a context teeming with helpful ideas and alternative solutions."

This general view differs little from Cameron's analysis of the specific example of dialysis (Cameron 2002, p28):

> "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. 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…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."

[36] Cameron (2002, p68) gives a rather different perspective, which is relevant to the later discussion of the resistance from the medical establishment to the introduction of dialysis: "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 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 the German professors, with a major involvement in the study of renal disease, who declared at the meeting of the German Society of Internal Medicine at Weisbaden 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."

It is, however, difficult to assess to what extent the body of scientific knowledge relevant to dialysis (Table 2.3) was either known or considered useful by the inventors of dialysis[37]. Gilfillan, making a sociological analysis of innovation, specifically argues that invention is not necessarily based on prior science and, indeed, "it often precedes or evokes apposite science" (Gilfillan 1985).This is not to say that Kolff, Alwall and Murray were ignorant of the *clinical* science of uraemia and its toxins, but rather that they regarded the *basic* science as peripheral to their clinical and technical problem solving. The obverse of this is that laboratory scientists did not realise the potential clinical application of their *in vitro* knowledge[38].

Eden questions the motivation for invention (Eden 1984): "How do new developments come about? Logically, the process must begin with the recognition of a need…" (p53) and suggests that it is physicians, by recognising a therapeutic or diagnostic need, who provide the innovative impetus. "The clinician, as the principal health care provider, is the person most likely to recognize the need and to state the problem in the medically appropriate context." (p61). But "…careful evaluation does not invariably, or even often, precede research and development." (p53). It is well documented that, certainly for Kolff and Alwall, the critical stimulus to develop an artificial kidney was their sense of frustrated impotence when faced with a particular patient dying of uraemia (Kolff 1965; Alwall 1986; Cameron 2002; Heiney 2002). Their *personal* reaction to this therapeutic hopelessness was to devise a practical solution to a specific clinical challenge, a solution which was largely independent of the knowledge that was embedded in their scientific background.

[37] Cameron 2002, p71: "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…and the way they approached their…experiments show they must have been largely ignorant of this body of work. It seemed that the knowledge that urea…could be dialysed…was enough to satisfy them that they were on the right track."
Peitzman 1997, p300: "The early kidney makers struggled with typical inventors' problems – finding materials and configurations to make an envisioned machine work. They sought an arrangement to run blood on one side of a membrane and a dialysate (then called 'rinsing solution') on the other, in such a way as to maximise the surface area of the membrane and minimize the volume of blood in the filter. And the affair must not leak, clot, or explode."

[38] Eden 1984, p51, referring to the vividiffusion experiments of Abel, Rowntree and Turner: "…their intention was to develop a pharmacological research tool. So far as we know, they were not motivated by a perceived need for a therapeutic device. Indeed, it may not have occurred to them that their device could have a therapeutic application." Cameron states that, a decade or more later, Abel did propose that his device could be used for treating kidney failure, but this was after the work of Haas and Necheles had been published and, allegedly, after he had declined to help with a patient with mercuric chloride-induced acute renal failure.

A particular example of the dissociation of basic science and practical invention is provided by the concept of the 'toxins' which accumulate in renal failure. The nature of uraemia had long been a subject of investigation (Table 2.4) and it was known that whilst urea is the most readily identifiable and measurable metabolite that accumulates, there was actually little evidence that urea *per se* was toxic. Although laboratory scientists continued to seek *the* uraemic toxin (a quest that continues today), the pragmatic inventors were content to accept that kidney failure as a whole was 'toxic' and, further, that whatever the nature of the chemical mediator(s) of this toxicosis, it (they) must be water soluble (to be excreted in the urine) and therefore amenable to removal by dialysis across a semipermeable membrane using water-based dialysate.(The concept that the kidney might have functions other than excretion of water, electrolytes and nitrogenous waste products did not properly impinge on the scientific consciousness until the long-term maintenance of patients by the *partial* treatment with dialysis revealed the full complexity of the syndrome of chronic renal failure – for example, failure of synthesis of vitamin D or erythropoietin). Cameron (2002, p20) alludes to this dichotomy between the theoretical basis of science and invention:

> "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…"

Cameron's analysis is supported by Kolff himself, who despite his academic credentials took an entirely empiric view:

> "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. The clinical improvement of our patients proves that the substances responsible for the syndrome of uraemia are removed by dialysis." (Kolff, 1947, p77)

If the basic science of dialysis and uraemia appears not to have been prominent in the thinking of the early users of dialysis, then their emotional involvement in the patients, the disorder and the machine deserves further consideration. Many cited cardinal patients as the motivation for innovation, invoking a sense of frustration and therapeutic impotence when faced with untreatable cases. In the next chapter, doctors' dependence on cases for their thinking and understanding is further discussed. It is, however, possible to over-stress the symbolism of the iconic patient galvanising the innovative doctor into heroic action. It is noteworthy that all those describing a damascene moment

did so many years after the event, and for at least some the motive might have been an attempt at *post hoc* justification of their actions. For example, Thorn of the PBBH in an interview with Peitzman (Peitzman 1996) described a seminal case which directed his subsequent practice (Thorn 1981). The story is so exceptional that it is considered in detail. In 1947, a young woman was referred to the PBBH with ARF following a septic abortion (even decades later Thorn studiously avoided using these words although it was clearly an illegal abortion). On the 10^{th} day, she became comatose and, in the absence of any other useful intervention, they decided to perform a renal transplant (i.e. the first recorded attempt in humans). The donor was a member of staff's husband, terminally ill with leukaemia. Surprisingly, the kidney briefly produced urine and a few days after it ceased to function, the patient's own kidneys recovered function. 20 years later Thorn said "this remarkable experience dramatized the need for a practical means dialyzing…if significant progress were ever to be achieved…" Setting aside the many debatable issues generated by this case, it can be seen that Thorn retrospectively used it as an example of therapeutic desperation justifying his early forays into dialysis.

Although many, especially Kolff (Kolff 1965), cited individual desperate cases as the stimulus for innovation, it is equally possible that unfortunate experiences may inhibit the acceptance of a new procedure. Presumably most such are not reported, but there is an illuminating case (Fishman, Kroop et al. 1949) from the Mount Sinai Hospital New York, where the first dialyses in the USA were performed. The details of this pivotal case illustrate that acceptance of an innovation may be determined by emotional as well as technical experience. Following a rape, a woman induced abortion with a large dose of mercuric chloride tablets. She became critically ill with ARF due to a combination of mercury intoxication and septic abortion. A single six-hour haemodialysis session produced a marked symptomatic improvement and she went on to make a full medical recovery. However, as she improved physically it became apparent that she was severely psychiatrically disturbed, eventually necessitating her long-term committal to a State mental facility. Her physicians were unable to satisfy themselves as to whether her psychiatric state preceded or was induced by her acute illness and its treatment. This deeply troubled all those involved, the concern being that a technical success may in some way have induced an insurmountable problem. From being the first to embrace haemodialysis in the USA, the Mount Sinai group became strong advocates of the conservative management.

2.4 Adoption and diffusion of dialysis

The early dialysis machines were cumbersome, inefficient, extremely difficult to use and, above all, dramatically unsuccessful. A new procedure which carried 94% mortality would be unacceptable today, but the social environment of the 1940s was quite different. Cameron (2002, p91): "How different from the 1940s, when Kolff could say 'nobody ever tried to stop me'; empiricism had the major role – and the patient no voice." There was simply no institutional overview, legislative control, or ethical policy. The doctor's decision was final, his opinion and actions unchallenged – a social attitude that was endorsed by the public and with the collusion of patients[39].

Cameron has, to some extent, compared the circumstances obtaining in the 1940s and 1950s with the legislative, ethical and conceptual environment of today: "It is interesting to reflect now what would happen today if a new, potentially hazardous treatment were tried for so long and so unsuccessfully…" (Cameron 2002, p79). Further (p91), he suggests that dialysis could not be introduced into modern clinical practice and cites the following reasons: extensive animal experiments would be required, but dogs are difficult to keep alive on dialysis because of coagulation problems – "such a programme would almost certainly be judged a failure"; it had been known since 1936 that cellophane activates complement, which would ensure that there would be a demand for a 'biocompatible' membrane (only partially achieved today); the use of urea as a surrogate marker of uraemia and of dialyser efficiency would probably be judged invalid and so would require the identification of specific uraemic toxins (not yet achieved); the colossal research and development costs, together with the limited identifiable market, would have precluded the development of dialysis, a point highlighted by other authors[40]. It is, of course, the case that the invention of dialysis was funded either by the individuals themselves (Murray, Kolff) or by their institutions (Alwall). Commercial R+D did not appear until more than a decade later and governmental funding hardly at all. Governments did begin to formally fund treatment, thereby expanding the market in which commerce found investment to be worthwhile. Significant industrial involvement

[39] Peitzman, 1997 (p299): "the shared context of the 1940s was a period of medical freedom, with no formalised bioethics or supervision of clinical research." "They were not opposed or regulated by any higher authorities and proceeded as they thought best."

[40] Eden, 1984, p59: "…when a device has only a small market – perhaps for use in the therapy of a relatively rare disease – it is not likely to be developed. If the need is perceived by the public and the decision makers is sufficiently great, its development will be subsidized…[T]he case of the artificial kidney: the treatment is so costly and the need so obvious that both development and therapy are almost completely underwritten by the federal government." Eden is almost certainly incorrect in his analysis, as development (as opposed to therapy) costs have received little or no direct government subsidy.

followed the development of large scale treatment for ESRD, effectively from the 1970s. As will be seen later, the development of dialysis clearly demonstrates Eden's statement (1984, p58) that:

> "Industrial innovation is limited largely to the development of modifications and improvements in technologies whose principles and practice are already fairly well understood."

Although undoubtedly "…technology does not arrive at the bedside with its meanings already determined but, rather, ideas about how…tools can be used reflect a social context as well as a technical function." (Howell 1995, p229)[41], it is clear that in the case of dialysis the use for which it was intended by its inventors failed for practical reasons but, serendipitously, embedded within this failure was a success that allowed dialysis to come into clinical use, and to survive until a technological development later allowed its originally intended use. By their own admission "…both Kolff and Alwall 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…" (Cameron 2002, p110). However, when applied to chronic renal failure, the technique was a failure, achieving at best some transient symptomatic amelioration but requiring repeated application which was impossible because of vascular access problems. Thus it was that Kolff's seventeenth patient had *acute* renal failure, was successfully treated and allowed Kolff to publicise his achievement. Thereafter, during the period of diffusion of dialysis, the technique became limited to the treatment of patients with acute, potentially reversible renal failure[42]. There was, therefore, a coincidence in the later 1940s of a procedure, inadequate for its intended purpose but apparently effective in the treatment of a newly-recognised and expanding condition, acute renal failure.

The step between a handful of patients in a few isolated sites and a global routine treatment for tens of thousands is not immediately obvious. The diffusion (Banta 1984) and acceptance of new medical technologies has received wide attention in the sociological and historical literature, and in many ways dialysis is a better exemplar of these concepts than are some of the technologies studied. McKinlay's concept of the

[41]Koenig 1998, p470: "The meaning of a new technology is not automatic, but evolves gradually."

[42]Cameron 2002, p188: "John Merrill has testified to the fact that by the 1960s almost all physicians had become blinkered and considered dialysis in the short-term only…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…"

seven stages of the progress of a medical innovation (McKinlay 1981) may provide an useful framework on which to hang the career of dialysis, but it should be remembered that the major disadvantage of the scheme is its rigidity, which suggests that more order and coherence exists than is actually the case. "To invent something is only to offer society a possibility; society can still decide whether the possibility offered is worth implementing or not." (Westrum 1991, p160). The first stage of acceptance or implementation (McKinlay's 'promising report') is the advertisement and promotion of the technology by its 'champions' (usually, but not invariably, its inventors), a process critically dependent on communication. McKinlay highlights the role of media reports ("These promising media stories usually report activities that meet no methodological criteria whatsoever", p378) and preliminary case reports in medical journals, which rarely if ever report unsuccessful interventions making them in McKinlay's opinion "inferentially worthless", being no more reliable than media reports and "certainly have no value as a basis for social policy" (p399). Koenig (Koenig 1988), in her essay on the 'technological imperative', discusses how early optimistic reports of medical innovations are uncritically received (p488) and consequently "new treatments commonly diffuse into widespread clinical practice before evidence is available about their actual usefulness" (p467). In the case of dialysis, the media were used very effectively by the proponents of the treatment, both in the UK and the USA, but at a later stage, not at the first introduction of the technique. Kolff deliberately chose to publish his early report in *Acta Medica Scandinavia* because the journal was published in English in a neutral country and was available in the Netherlands and the non-German-occupied world (van Noordwijk 2001, p49).

As Arnold Relman[43] emphasised (Relman 1980), doctors have a position of economic primacy in determining patterns of resource utilisation. They are influenced by personal contact and, to a lesser extent, by publications and then in turn they influence institutions. It was by personal communication that Kolff brought his machine to the attention of the medical world. It is Kolff's energetic personal advocacy of his device that perhaps partially explains an anomaly in the introduction and development of dialysis: from a 60-year perspective it is hard to explain the dominance of Kolff's rotating drum dialyser which, despite subsequent modification by the groups at the Peter Bent Brigham Hospital Boston, the Necker Hospital Paris and at Leeds, was in many

[43] Arnold Relman (b1923): Professor of Medicine at Harvard and highly influential editor of The New England Journal of Medicine, 1977 - 1991

ways technically inferior and certainly more difficult to use than many if not most of the competitor systems[44] that rapidly appeared in the decade after the Kolff machine came into use (Table 2.5). The difficulty, not to say drama, of performing a dialysis with the Kolff machine has been well attested (McBride 1979; Drukker 1989; van Noordwijk 2001; Cameron 2002) and is eloquently described by Cameron (2002, p115):

> "None of these procedures was easy to perform. A haemodialysis session was more of an adventure than a controlled form of treatment: Kolff's rotating drum dialyzer, in particular, was clumsy, huge and so powerful that 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."

In fact, it was not until 1956, with the commercial manufacture of Kolff's later invention of the disposable coil dialyser, that the supremacy of the Kolff drum was seriously challenged[45]. As Westrum (1991, p158) has discussed in the context of technological innovation, a salient feature of the creative personality is self-confidence. Undoubtedly, Kolff was not only an inventive genius (his achievements included not only dialysis developments, but also an effective blood-banking system in Rotterdam during the German invasion, and also the first usable artificial heart), but he also had the confidence and determination[46] to surmount considerable difficulties to develop and promote his ideas. Kolff's advocacy must be the main reason why he is regarded as the "titular inventor" (Peitzman 1996, p276) of dialysis.

The first stage of diffusion[47], the process whereby a medical technology enters and becomes part of the health care system, involves awareness, that is to say the period during which a potential adopter learns of the innovation and acquires some knowledge about it[48]. It is clear from a variety of sociological studies that personal contact with, and

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[44] The Alwall device, whilst technically superior particularly in its control of fluid removal, was also extremely cumbersome and difficult to use, and a number of units tried it and abandoned it. Alwall had the opposite character to Kolff – quiet, reserved.

[45] Peitzman 2001, p201: "The disposable kidney system could be made ready for use fairly quickly, while the older systems…demanded slow and tedious setup procedures." "In the United States, Kolff-Brigham rotating drum machines, much like steam locomotives (which they somewhat resembled), entered museums or were scrapped, although some continued to spin away in other parts of the world where labor was cheaper than disposable supplies. The presterilized throwaway kidney made dialytic treatments much easier to prepare and perform, while its similarity to the already familiar disposable hospital supplies further helped dialysis seem routine. In fact, during the 1950s and beyond, disposable goods were becoming an emblematic part of American life, not just of hospital practice."

[46] Peitzman 1996, p276: "Kolff's kidney building showed zealous perseverance and ingenuity played out in an environment of uninhibited medical – though not political – freedom."

[47] "a very agreeable word to apply to the history of dialysis" (Peitzman 1997, p305)

[48] This section draws largely from Banta (1984), who in turn develops arguments from Rogers EM, Shoemaker FF. 1971. Communication of Inventions: A Cross-Cultural Approach. New York: Free Press

advice and endorsement, from 'leaders' in particular fields are a very important, if not the most important, factor in facilitating adoption of innovation. The corollary is that objective evidence from controlled randomised clinical trials is of less significance and, indeed, has been repeatedly shown to fail to influence practice. It is relevant to note here that dialysis was introduced before 'evidence-based medicine' became *de rigueur* and that it has never been subjected to any form of rigorous examination[49].

Kolff's advocacy of dialysis has the appearance of a personal crusade, although it is far from clear whether this arose from a desire for promotion of himself and his device or from an enthusiasm for the procedure in which he had invested so much of himself. Nor is it clear from his biographers, all of whom take an optimistic if not sycophantic view, how much of Kolff's efforts during the late 1940s were a deliberate attempt to exploit the attitude (specifically in the USA) then prevalent of technological optimism in medicine, or whether he merely responded to opportunities presented to him by others. What is beyond doubt is that he displayed remarkable personal generosity, both then and since, in that with all his inventions he deliberately avoided personal financial gain by patent protection and he freely gave of his ideas, methods and even detailed drawings and plans. In a unique act of generosity he had, by the end of the war, constructed

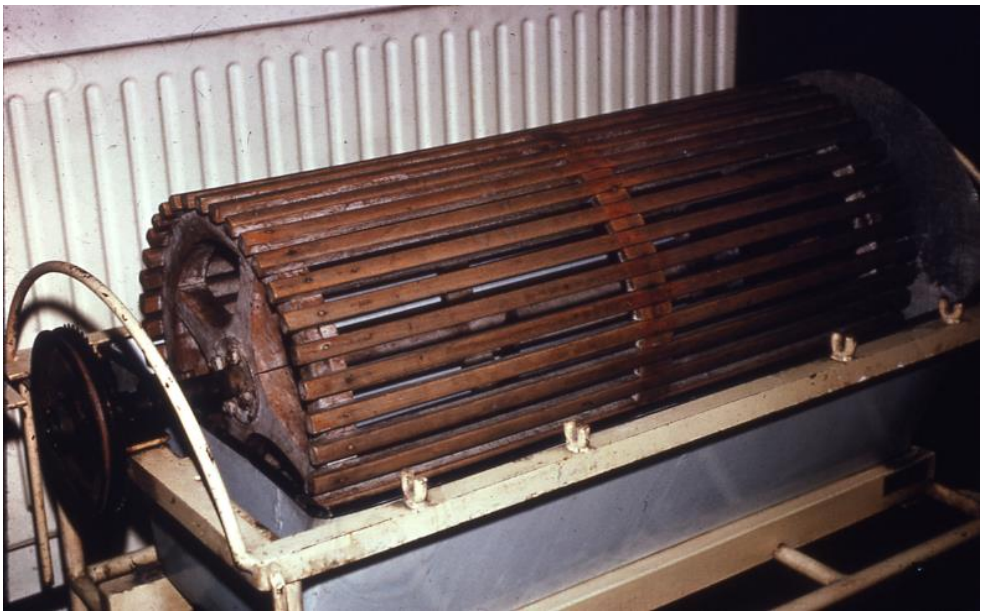

Figure 2.8. Hammersmith Kolff Machine

several additional machines which he, immediately on cessation of hostilities, donated to the Mount Sinai Hospital New York, Hammersmith Hospital London, Royal Victoria

[49] In reference to Scribner's introduction of long-term dialysis, Cameron (2002, p191) states: "No controlled randomized prospective trials or meta-analyses were done, or were needed."

Hospital Montreal, and others were sent to Amsterdam and Krakow Poland. The Dutch and Polish machines were never used (Drukker 1989, p33), particularly in Amsterdam where Professor Borst became one of the leaders of the 'conservative' backlash against dialysis, and dialysis was not reintroduced there until 1959. At the Hammersmith, AM Joekes (who was a distant relative of Kolff) and his colleague Eric Bywaters (who had described the crush syndrome) visited Kolff at Kampen immediately after the war "and with characteristic generosity Kolff came to London and gave them a rotating drum kidney" (Cameron 2002, p120). This machine was used from October 1946, making the Hammersmith group the third in the world to perform clinical dialysis[50]. The Montreal kidney was used by Nannie de Leeuw, who had worked with Kolff in Holland during the war. This personal connection in the dissemination of dialysis was continued by Jacob van Noordwijk, Kolfff's chief assistant in Kampen, who also emigrated to Canada, establishing dialysis in London, Ontario in 1949.

Bywaters was not the only visitor to Kampen: interested physicians from Canada, France and elsewhere were enthused by Kolff, given plans for the construction of the dialyser, and returned home to further spread the word. By far the most significant connection was with the Mount Sinai Hospital, where the professor of medicine was Isidore Snapper, a Dutch Jewish émigré. Not only did this group, which included yet another of Kolff's trainees[51], perform the first successful dialyses in the USA[52] (Cameron 2002, p 134) but also, sponsored by Snapper, Kolff made several visits in 1948/9 when he lectured and gave demonstrations. The flow of ideas was not unidirectional. Gordon Murray in Toronto had limited success with his machine, in part because of local apathy or antipathy[53], but also because Murray, who was a successful

[50] "The earliest renal dialyses in this country were therefore undertaken at the Hammersmith under the auspices of the MRC." (Booth 1989). (The significance of this for the adoption of dialysis in Britain will be explored later).

[51] Peitzman 1997, p300: "[Kolff] also found positions for several of his coworkers, thus effecting emigration of men and machines." Peitzman quotes from Connor J. 1994 Dutch technological migration and North American commercial exploitation: Dr Willem Kolff and the development of the artificial kidney. In: Holfte R, Kardux J, eds. Connecting Cultures: The Netherlands in Five Centuries of Transatlantic Exchange. Amsterdam: Free University Press, pp 139 – 159.

[52] McBride (1979, p19) reports that the Mount Sinai experience was not altogether plain sailing: "… the first dialysis in the United States had to be postponed when a spontaneous diuresis occurred caused by the patient [who had mercuric chloride poisoning] seeing the formidable equipment." "…this radical form of therapy met with resistance from the hospital staff. Use of the kidney was permitted only…after the normal surgical schedule was completed. Frequently, the gallery would be filled with observers dressed in tuxedos and evening gowns, who had returned to the hospital after dinner or the theatre to watch the novel procedure."

[53] Cameron 2002, p83: "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."

surgeon, was turning his attention and personal resources to the development of heart valves. Nevertheless, a visit to London evoked much interest[54]. Kolff was in communication with Murray and Alwall, sending the latter Visking cellophane tubing and visiting Lund in 1949. In Germany, despite his previous opposition to dialysis, Volhardt contacted Alwall, who visited Munich but only after Volhardt had died. Germany was very late to adopt dialysis and never used a Kolff-type machine.

Murray abandoned renal work: he was entirely self-funded, had no staff to supervise dialysis and could not afford to spend time away from his surgical practice; in 1952-3 he designed a sophisticated flat-bed dialyser, the designs for which were stolen by a visiting clinician and it subsequently went into commercial production in Germany. "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" (Cameron 2002, p85). Despite his many achievements (original work on heparin, dialysis, clinical transplantation, cardiac surgery), Murray's career ended in disgrace (at the age of 72) because of falsified claims relating to cancer immunotherapy and spinal cord surgery. Alwall, despite widespread recognition resulting from his numerous meticulous publications, only slowly persuaded his Swedish colleagues to consider dialysis[55]. Alwall had established a kidney unit in Lund in 1947, the next was in Umea (in the far north) in 1958, and dialysis did not reach Stockholm until 1960 (Cameron, 2002, p120). Kolff himself fared the worst. In Holland there was strong opposition to dialysis led by Professor JGG Borst (1902 – 1975) of Amsterdam who, with Bull of the Hammersmith, became the leading protagonist of the conservative management of acute renal failure[56]. A Kolff rotating drum was used transiently in Nijmegen in 1949 but dialysis only continued in Rotterdam (under Dr EE Twiss, a pupil of Kolff's) until it was reintroduced to Amsterdam in 1959 by William Drukker. "Such was the opposition to his ideas in the Netherlands that in 1950 Kolff emigrated to Cleveland…" (Cameron 2002, p120). He received little support there and only resumed his inventing career after moving to Salt Lake City (Heiney 2002).

[54] Cameron 2002, p83: "Murray was invited to lecture in London in 1949…on the artificial kidney and its use. This aroused much interest, despite, perhaps because of, the fact that dialysis was in abeyance in the United Kingdom. In 1949 also Kolff came to Toronto and met Murray." (BMJ 1949; 2: 887-891).

[55] "During the 1950s, patients were said to have been 'Alwallised' if they received dialysis treatment, with the implication that this was a prelude to burial." (Cameron 2002, p120)

[56] "Borst boasted that their artificial kidney – donated by Kolff – was rusting in the attic unused, because it was not needed." (Cameron 2002, p120)

The centre of dialysis had moved firmly to the USA, where the attitudes and financial resources were more conducive to medical innovation than they were in Europe[57]. A key event for American nephrology appears to have been Kolff's demonstration in early 1948 of his 'rotating drum' kidney by invitation at Mount Sinai Hospital in New York City. "Several physicians came to see the Dutch inventor's awkward but promising contraption…Subsequently the 'Kolff-Brigham' refinement of the rotating drum established Boston as a centre of dialysis…" (Peitzman 1988, p225)[58]. Thorn directed the Electrolyte Division at the Peter Bent Brigham Hospital and Merrill, a patrician Bostonian resident working on electrolytes in cardiology, was put in charge of the renal failure programme. Whatever the precise details, it is arguable that without the personal contact between Kolff and the Boston group, dialysis would simply have faded away. The PBBH group, especially Merrill, became highly influential and again personal contact was a key factor – for example the two most important French renal centres started dialysis after visiting Boston and after a reciprocal visit to Paris by Merrill (who was, unusually, both Francophile and Francophone)[59]. Parsons of Leeds was introduced to dialysis by Merrill[60], as was Scribner. The PBBH had been deliberately founded and structured to foster clinical research and during the 1940s and 1950s was arguably the leading US research centre. The electrolyte division was at the heart of the hospital's activities, vigorously researching endocrine and metabolic disorders (Fox 1998). Thorn, who later admitted that his interest in renal disorders had also been stimulated and

[57] Peitzman 1997, p302: "The post-war disruption and financial struggles in Europe did not favour serious investment in a seemingly bizarre and complicated device, whereas in the US, a certain degree of prosperity coupled with a cultural embrace of science and its potential, which many persons understood as 'machines', favored development of dialysis."

[58] Peitzman (1988) and McBride say that George W Thorn (1906 -2004) and John Putnam Merrill (1917-1986) of the Peter Bent Brigham Hospital, together with George Schreiner of Washington, visited Kolff at the Mount Sinai Hospital. But Peitzman later (1996, p277), based on interviews with Thorn, says that Thorn invited Kolff to Boston, where he provided the blueprints of the machine.

[59] Cameron 2002, p125: "…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 agreement with Merrill's concept of total care of the uraemic patient rather than just concentrating on the dialysis procedure itself."

[60] Scribner (Scribner, B. H. (1990). "A personalized history of chronic hemodialysis." Am J Kid Dis **16**: 511-519.) attended a lecture by Merrill at the Mayo Clinic in July 1950. "Merrill's talk convinced me that the artificial kidney had a real future, both as a therapy and as a research tool to manipulate electrolyte balance. The Mayo Clinic did not share my enthusiasm." Scribner moved to Seattle, where he was "able to convince the VA research program that an artificial kidney was just what was needed…In 1953 they even sent me to visit several centers…" (p511). Scribner, of course, went on to revolutionise nephrology by starting treatment for end-stage renal failure in 1960.

maintained by his failure to treat individual patients[61], not only directed the introduction of dialysis but also the first clinical (live-related) kidney transplants. The achievement of the Brigham group was, firstly, to apply their scientific investigative culture to the study of acute renal failure, resulting in publications which were highly influential in delineating the natural history of ARF (Swann and Merrill 1953) and demonstrating the efficacy of dialysis (Merrill, Smith et al. 1950; Merrill, Thorn et al. 1950)[62]. Secondly, and in the long-term more importantly, they created a *team* for the *total* management of patients with renal failure – active and conservative, dialysis and transplantation. The team included nurses, technicians, surgeons, engineers, and physicians, and was the model for all later renal units. Treatment was not limited to the artificial kidney, but included meticulous management of fluid-electrolyte problems, diet, and medical complications as well as exploring alternative/complementary treatments such as peritoneal dialysis and kidney transplantation. Initially, a surgeon Carl Walter[63] employed an engineer Edward Olsen (the "enabling artificer", Peitzman1997, p301) and together they ironed-out many of the problems of the Kolff machine, making a somewhat more amenable and efficient device. The resulting 'Brigham-Kolff' artificial kidney became the US standard, and was manufactured and exported in some quantity, including to Leeds (see Table 2.6). The Brigham group rapidly became highly influential and, together with colleagues who took the Brigham-Kolff to the Korean War, established the clinical utility of dialysis[64].

Thus the PBBH created the first dialysis *unit* (so named in the report of the Physician-in-Chief in 1951), thereby setting an organisational pattern that was eventually either copied or convergently evolved throughout the world, and remains the conceptual

[61] Peitzman 1996, p277: "What kept Thorn and his team going through that initial discouraging phase? It was the impetus from 'the single case', the potential for saving one identified patient under one's care when no alternative form of therapy was available. "I took risks", Thorn admitted decades later."

[62] Cameron 2002, p119, fn 18: Merrill's 1950 paper showing a better than 50% survival in a large series of ARF "did much to turn the tide of opinion in favour of haemodialysis after the rather dismal results in earlier patients."

[63] Carl Walter (1905-1992) modified the Kolff artificial kidney at his own expense. He had experience of plastics as a pioneer of blood transfusion technology and had founded Fenwall Laboratories, which commercially developed medical plastics.

[64] Marks 1993, p1594: "Clinical utility is as much a product of historical events as an inherent property of the technology." "…clinical utility is (in part) socially produced…value could only be established by advocates…who had the requisite enthusiasm for the product, sufficient patients on whom to assess and demonstrate the instrument's worth, and the opportunity to 'train their fellow clinicians in a new way of thinking and looking'."

framework for integrated renal units today[65] – Peitzman's "salons of depuration of chemically unclean bodies". The spatial and organisational reconfiguration required to create a 'unit' acquires social significance: it implies acceptance of the technology as it becomes embedded in an institutional structure, it reinforces the identity and uniqueness of the machine and those who tend and control it, and it is an essential stage in the 'routinisation'[66] of an innovation. This is not to say that, in the early 1950s, dialysis was not firmly at the left-hand end of Koenig's axis of experimental-standard therapy[67] or Fox and Swazey's experiment-therapy continuum (Fox and Swazey 2002), indeed it would probably be a quarter of a century or more before dialysis became a recognisably 'routine' or conventional therapy. However, the Brigham unit did formalise the management of renal failure and place it firmly in the ambit of the 'specialist', this identity being reinforced by the establishment of similar organisational structures elsewhere[68].

Whilst the Brigham unit came to be regarded as a beacon of rational success, at the time the general situation was, at best, anarchic[69]. The period of the early 1950s might be described by McKinlay's second stage[70], professional and organisational adoption, or Branta's second phase: that of trial. More realistically, the scene resembled the

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[65] Marks 1993, p1598: "The literature on technological change clearly instructs us that innovation presents repeated opportunities for changing the organization and content of medical work. It is less clear how, when, or why some possibilities become reality and others do not."

Peitzman 2001, p201: "There were other indicators by the mid-1950s that the artificial kidney had a future. In a few centers it acquired a home of its own when space was assigned for a 'dialysis unit'…In such a unit – itself an invention – dialysis might proceed routinely and efficiently; it no longer seemed an extraordinary adventure."

[66] Koenig 1988, p469: "The use of a new therapy upsets the everyday routines of clinical practice…Over time, however, this upset must resolve…Medical procedures which are not abandoned in the earliest stages of use eventually proceed to a state of 'ordinariness'. Their use is no longer perceived by hospital staff and patients as unique and new. They become the standard of care."

[67] Koenig 1988, p470: "…the placing of a machine along an axis of experimental versus standard therapy…occurs as participants in the use of the technology struggle with its application and gradually tame the machine through a process of routinizing its use in everyday practice." "Before too long…machine users developed strategies to keep up at least 'the appearance of normal operations'."

[68] Bennett 1977, p127: "Technologies require new housing, new technicians, and new bureaucracies and systems of organized behaviour."

Scott 1990, p166: "Innovation within medical care units is…likely to reflect an organizational or even an interorganizational process rather than an individual process."

[69] Cameron 2002, p138: "In contrast, 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 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."

[70] McKinlay 1981, p381: Adoption "denotes a unique relationship with the innovation: the act of formally accepting and taking up some activity and using it as one's own, without the idea of its having been another's – to embrace or espouse it."

'desperation-reaction' model of diffusion (Warner 1975). Clearly this can be seen as a prime example of 'technological imperative' ("the mere existence of a dramatic new medical device provides a mandate for its continued use" Koenig 1988, p465), a term coined by Fuchs and developed by Koenig (Fuchs 1968; Koenig 1988). But most commentaries on medical technology do not consider a situation comparable in degree to that of dialysis in this period ("the roaring fifties"(Schreiner 1990)), although there is some analogy with the evolution of markets for technology[71]. Perhaps Cameron (2002, pp 992-3) best summarises the confused and confusing situation:

> "…reality is 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…whilst technology had much to contribute to the evolution of dialysis, empiricism had an even greater role to play."

Few understood Merrill's wise counsel on dialysis:

> "The successful operation of an artificial kidney requires more than the possession of the apparatus, and its successful use depends on the skill and experience of the operator."(Merrill 1957)

The somewhat chaotic situation in the 1950s may be related to four factors:

- a plethora of 'do-it-yourself' dialysis systems (Table 2.5)
- inappropriate use of dialysis
- confusion over what *type* of dialysis should be used
- growing resistance to the use of dialysis.

Once dialysis had begun to be noticed by the medical community, technologically-minded Americans immediately started developing and improving dialysers. Whilst some devices displayed considerable ingenuity, none were ever adopted other than by

[71] This has been analysed in a narrow sense by Westrum and relates to his 'generative burst': a large number of firms enter the market and "the technologies generated in this phase are accordingly diverse, incorporating divergent and often contradictory subsystems." (Westrum 1991, pp196-199) It is perhaps to overstretch the commercial analogy in the context of the non-commercial conceptual marketplace of early dialysis.

their inventors[72]. Some concepts reappeared in a refined form when industry later entered the dialysis field. This widespread individualised creative invention may perhaps be unique to dialysis, but it is difficult to understand why this may be so. An extraordinary number of individuals, mostly surgeons, constructed their own dialysis machines. Was this an expression of disillusionment with the available technology, or did each feel that they had an unique contribution to make? Whatever the motivation, it challenges the assumption that potentially treatable renal failure was as uncommon as generally assumed at that time. The expense and complexity of existing machines would undoubtedly have put off some who might otherwise have been tempted to try dialysis. As the clinical indication for the use of dialysis was widely perceived to be an unusual occurrence, most institutions felt little need to purchase a machine. Further, as dialysis was far from universally accepted, there was little institutional kudos to be gained from providing this service. Whatever the reasons, a large number of home-made devices appeared and then vanished. Peitzman (1997, p301) summarises the situation thus:

> "The kidney machine builders seemed a throwback to an earlier style of inventor – the determined mechanic in a basement workshop. Once commercial manufacturing of dialysis equipment began, successive improvements emerged largely from industrial development, with physician participation: this remains the invention model for the 20th century."

2.5 Industry

It is perhaps here appropriate to consider the entry of industry into the dialysis arena, an entry that was as hesitant and fitful as the emergence of dialysis itself. In the partially analogous history of total hip replacement (Anderson, Neary et al. 2007), the globalisation of the procedure was driven by the entry of (predominantly American) industry after the technique had received clinical approval. The development and marketing of modified prostheses depended, at least initially, on close cooperation between clinician-inventors and commerce, the financial power of the latter proving crucial. For dialysis, commercial investment was slower and far more multinational, with major companies arising in Europe and Japan as well as the USA.

[72] Eden 1984, p62: "Many technologically successful projects that are described in the literature or stored in the files of research institutions never reach the health care practitioner because the innovators' enthusiasm outran their understanding of the market of their product."

In 1949, the Allis-Chalmers Manufacturing Co. Milwaukee designed a sophisticated Kolff drum of which 14 were made and sold in the USA. The stimulus for the company was provided by an employee with renal failure and no available machine. In 1950 Jernstedt (Pittsburgh) was contracted by the Westinghouse Corporation to design what was the first complete dialysis system - only three were made and were transiently used to treat paediatric cases[73]. In the mid-1950s, Kolff invented a new coil dialyser (Kolff, Watschinger et al. 1956). This was archetypal 'basement tinkering' invention: a cellophane blood tube, supported on the mesh from a fly-screen, wound round a pineapple juice can. Kolff persuaded the Singer Sewing Machine Co. to develop a machine that could sew together two strips of screening (McBride 1979, p43) and, after being rebuffed by other companies, took his device to Travenol Laboratories Inc., Morton Grove, Illinois (now Baxter Inc.).

Figure 2.9 Travenol Coils c 1956-60

The field of dialysis then changed irrevocably, and with it, so too did nephrology. Kolff had also developed, from a washing machine, a device with which the twin-coil dialyser could be used. In October 1956, Travenol marketed this dialysis delivery system, of which 123 units were shipped between 1956 and 1959, but nowhere near that number were used clinically – "In fact, few were even uncrated…" (McBride 1979, p47). The relatively slow sales of the Travenol dialysis machine reflects the then perceived need for the treatment of kidney failure. ARF needing dialysis was thought to be uncommon and could be accommodated within the few specialist centres. 1960 saw an abrupt change with the introduction of the Scribner shunt and the subsequent treatment of ESRD patients. The addition of these chronic patients, together with an

[73] McBride 1979, p37: "…both companies believed that the potential market for these dialysis units was extremely limited."

increasing frequency (recognition?) of ARF stimulated demand so that by 1961, nearly 250 hospitals in the USA had the Travenol system (Peitzman 1996, p280). As part of the commercial package, Kolff provided training in its use, sponsored by Travenol. A later version (the '200l tank') was in widespread use worldwide at least until the late 1970s[74]. "Almost surely a catalytic development was the disposable dialyzer" (Peitzman 1996, p280). The pre-sterilised twin-coil dialyser made dialysis easier to prepare and perform and the similarities to hospital disposable supplies which had become increasingly familiar through the 1950s "further helped dialysis seem routine" (Peitzman 1996, p280).

The US military also provided funding and facilities for the early investigation of dialysis, but this appears not to have made the transition to commercially-marketed technology. The extensive experimental work (and, later, occasional clinical use) on peritoneal dialysis by Seligman and others was commissioned by the Navy Department during World War II, the bureaucratic rationale for this support not being recorded; that is to say, it is unclear whether the Navy, in contrast to other branches of the military, recognised the significance of post-traumatic acute renal failure. This line of research appears not to have been pursued by the military after the end of the initial contract with the academic department at Mount Sinai Hospital. Macneill (MacNeill, Doyle et al. 1956) gives tantalising hints of military involvement in dialysis in a paper reporting the first clinical use of the "MacNeill Mark XIb" folded flatbed dialyser. He states that the device originated in 1942 with the design and construction of membrane blood oxygenators in "a military environment". Nothing more is known of these oxygenators (quite possibly because they appear to have been years ahead of their time without, as then, any clear indication for their use). MacNeill further states that the idea was resurrected for dialysis in laboratory experiments in 1948. The 1956 paper was supported "in part" by the Research and Development Division, Office of the Surgeon General, U.S. Army, but it is not stated whether this was research directed by the

[74] Like many nephrology trainees of that period (including Peitzman), the memory will always stay with me of pushing 'the Travenol' around hospital corridors to treat patients in ICU. It was the size and weight of a deep-freeze, on wheels like a supermarket trolley. In use, the drainage pipe was often hung out of a window, spraying everything below with a mixture of dextrose and uraemic metabolites. The dialysate in the tank would turn yellow as the metabolites were removed from the patient's blood – when the dialysate smelled too ammoniacal, you knew that a fresh batch had to be prepared (exactly as with the Kolff drum 30 years before). The machine may have been unsophisticated and clumsy, but it was very effective and could be used anywhere without the dedicated plumbing system of a renal unit.

military. The MacNeill device was not adopted by others, but was later used in modified form (Collins) by the military during the Vietnam conflict.

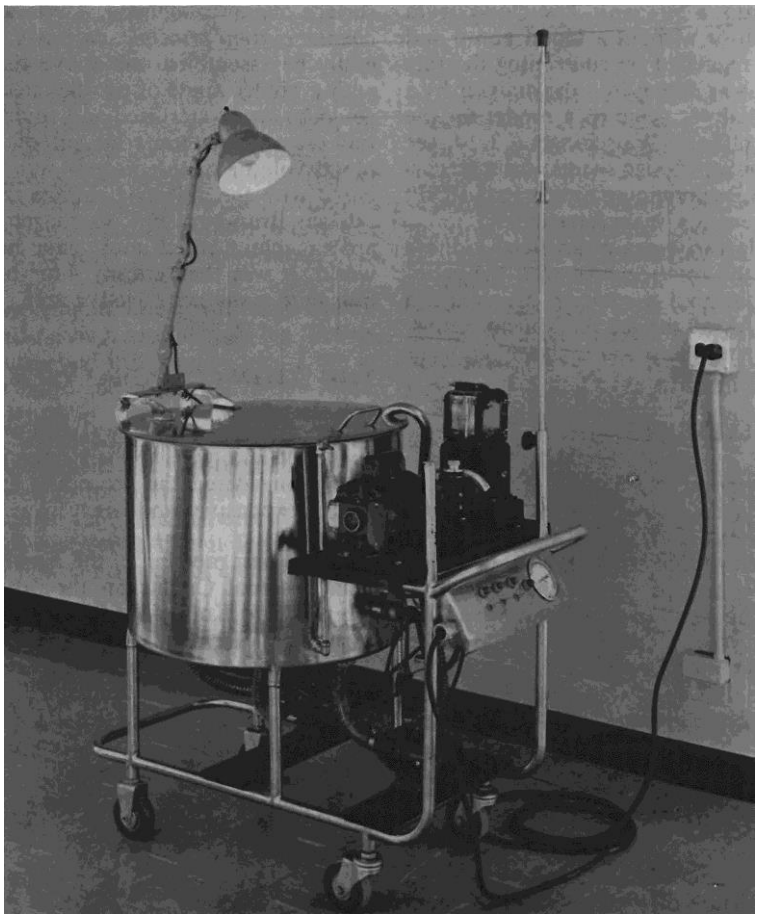

Figure 2.10 Travenol 200l Tank Dialysis Machine c. 1960

2.6 Qualified acceptance of innovation

It would appear from an extensive literature that a medical innovation inevitably elicits resistance to its introduction. The opponents of change are characterised as older, established, and fearful of losing status, power, influence or income. The proponents of innovation, conversely, are depicted as young, entrepreneurial, and seeking status and power. For the first decade or so after its invention, dialysis was vigorously opposed by influential figures within the medical establishment[75]. This aversity, perhaps uniquely for dialysis, drew heavily on the doubts of the advocates of the procedure. It is reasonable to infer that resistance to dialysis was both passive and active. By passive resistance, I mean that the concept that organ function could be replaced by a machine was radical

[75] The role of this resistance in delaying the implementation of dialysis in Britain is considered in detail later. This review will therefore concentrate on the USA where the divisions were greater and more durable.

and new and therefore difficult to absorb into the collective medical consciousness. This was not merely a technical development, it was a step-change in the application of therapy to a particular condition, and would have carried with it undertones of dehumanisation, substitution of personal care by impersonal gadgets, even a science fiction brave new world[76]. It was far removed from, even alien to, the experience of physicians brought up in the tradition of regimen and conservative passive treatment. Radical innovation required a major conceptual shift by its audience, who had not only to admit that what they (and generations before them) had believed, taught and done was, if not actually wrong, then inadequate, misguided and misintentioned; this has been explored in the literature hardly at all. The fear that instrumentation might come to dominate medical thought and hence 'dementalise' practice is longstanding (Weir Mitchell 1892).

Blume (Blume 1992; Blume 1994), in a longer and more general perspective, does touch on the ideological transformation that occurred during the 20th century that came to equate technology with quality medical care[77]. It should be remembered that at the time there were no nephrologists – dialysis was being offered to general internists who, whilst being familiar with X-rays and perhaps ECGs, would have been aware of the iron lung and blood transfusion as the only available therapeutic technologies, neither of which would have been likely to very much impinge on their working lives. Eden suggests that in the immediate post-war period, technological change outran both the depth and the generality of the scientific understanding of disease processes[78]. Whilst this may have been true in general (and the concept and the clinical characteristics of ARF were evolving in this period), actually for kidney physiology there existed a high level of sophisticated scientific understanding, at least in specialist academic centres. The development of ideas about ARF, the framing of this disease, ran concurrently with

[76] Cameron 2002, p221: "…the kidney [was] the first organ for which complete substitution…had been proposed. There was a deep suspicion of the idea that technology could replace vital function, and this feeling was present in almost all medical circles. Even so, the public at large was fascinated…"

[77] Blume 1994, p59: "…a gradual – and still more problematic – transformation took place at the ideological level. The gradual association of notions of quality in medical care with recourse to high technology and, related to this, the association of status in medicine with the use of advanced technologies, were accomplished only in the face of fierce resistance."

[78] Eden 1984, p50: "Although all of these facts [relating to slow diffusion of innovation] are relevant, probably the prime explanation is that the scientific basis for medical practice in both therapy and diagnosis was rudimentary. Medicine was still largely empirical. If medicine were to progress toward a more thoroughgoing scientific basis, it was necessary first to understand the processes of normal function and their pathologies at a fundamental level. Moreover, the evolution of technological devices intended to address a medical problem involves an interplay between the instrumental design and the state of scientific knowledge of that problem; this evolutionary process takes time."

the development of ideas about its treatment – and some of the key players in this story were contributing to both, an iterative reflective process that must surely have strengthened and legitimised their convictions[79] – what Metcalfe and Pickstone (Metcalfe and Pickstone 2006) have phrased an "autocatalytic" process[80]. On the other hand, the general physician of the time was deeply rooted in the "biographical way of knowing" in medicine (Pickstone 1994)[81]. It is therefore hardly surprising that the introduction of dialysis – a concept radically different from anything that had gone before, that is a machine that made a vital organ redundant, superfluous – evoked such a 'flat' response from the medical profession as a whole. Practitioners' attitudes and behaviours are conditioned by their shared contexts – education, background, personal experience, the state of society at a given time. Dialysis was a new way of thinking and of doing, and provoked an image of the possible with all the disturbing connotations that might bring. Banta (1984, p53):

> "The process of innovation in medical technology differs little from that of any other branch of application. But the complicated interaction of the many interested parties and their varying perceptions of an optimal strategy for innovation make the analysis quite different…"

Hostility to innovation is led by those already established[82], and the first line of defence is intellectual resistance, arising from failures of imagination (it is easier to see problems than solutions) or failure of nerve (fear of change) (Westrum 1991, p153). To this, particularly in a hierarchical profession such as medicine, must be added the defensive reaction which seeks to protect status and influence. Analysis of intellectual resistance is made difficult without the social context in which it arose[83]. We have seen how the newness of the technology had marched ahead of the scientific, intellectual and,

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[79] Jeffrey observed the same process in the development of cardiac pacemakers (1995, p584): "…the reciprocal and interactive process by which technological change and new concepts of disease stimulate each other, thereby creating a powerful momentum for growth."

[80] Metcalfe & Pickstone 2006, pp 154-155: "…knowledges and practices grew in autocatalytic fashion, as one problem led to another…an evolutionary adaptive process, constrained and encouraged by instituted relationships that co-evolved with the growth of knowledge and its application."

[81] Pickstone 1994, p16: "For many clinicians, experiment was an academic irrelevance. However, for some students, trained in laboratories, experimental science came to possess a clarity and direction beside which the world of real medical practice was but confusion."

[82] Howell 1995, p233: "Any change, any introduction of a new technology, threatens the status quo; what one group gains in power and prestige, another group loses. As new technologies become accepted, people who once based their expertise on skill and experience obtained without the new technologies find their contributions devalued."

[83] Westrum 1991, p152: "Many of these statements seem absurd in the light of subsequent experience, but they were delivered with great authority at the time, frequently by people whose opinions were very difficult to ignore."

indeed, emotional understanding of the general internist. The opposition from specialists is more specific and is structured on several levels. As Marks has pointed out, physicians arrogate supremacy over technology by claiming understanding of the patients and diseases to which the technology applies (Marks 1993). Further, medical critics who enjoy some specialty status, suggest that the dangers of new technologies result mainly from the thoughtless use of machines by other physicians. Only the rational informed doctor, whose intellect rules the device, is safe from being ruled by it.

Perhaps the most pervasive, and indeed persuasive, is calculative rationality which is based on empirical experience ("I know what works") and this is difficult to counter despite the fact that this rhetoric is fundamentally flawed: it assumes that circumstances do not change. Intellectual resistance then uses further elements of the rhetoric of denial (Westrum 1991), all of which were applied to dialysis:

- The proposed invention is impossible because it violates some scientific, clinical, or technical 'law';
- The inventors, being neophytes, are not competent; the true experts have already given up on the possibility of the invention, because it is either not possible or is unnecessary;
- Even if the invention were to be developed, it would be no more than of academic interest because it is either too costly or is directed towards a need that does not exist. (Here we stray into the thesis of social historians that specialties have invoked their technologies to define 'new' diseases to study and treat – undoubtedly true, at least partially, for dialysis for ESRD. Medical technologies create their own markets.)
- If the invention is developed, it would have side-effects which would render it worthless or even dangerous. (This was certainly a cogent argument against early dialysis).
- Alternative lines of development seem more promising. This was the main thrust of the arguments of the advocates peritoneal dialysis.

The rhetoric of denial is opposed by the generative rationality, the rhetoric of affirmation, of the proponents of innovation. It is hard to see how, when these battle-lines have been drawn up, any objective assessment of the worth of an innovation can ever be made. The concept of technological imperative is persuasive: simply to present a machine to the medical marketplace is sufficient to ensure its eventual use. A further point, perhaps specific to nephrology, deserves emphasis: the entrenched positions

regarding dialysis have been propagated, at least in the USA, as the "injurious divide"[84] between academic physician-scientists and pragmatic dialysis providers[85]. The basis of this intellectual resistance and the consequent division lies in individuals, their personalities and the power and influence they wield, particularly on those with whom they have personal contact.

At the time of the first attempts at dialysis, the most influential specialist in kidney disease was John Punnett Peters (1887 – 1956), director of the Chemical Division of the Department of Medicine at Yale. Not only was Peters unequivocal in his opposition to dialysis[86], but also he trained the majority of those destined to become chiefs of nephrology, who also "shunned or even condemned" dialysis[87]. To those nurtured in the tradition of laboratory medicine, whose status was assured by the huge post-war funding of research and teaching by the NIH and the Veterans Administration[88], the new-fangled *procedure* of dialysis appeared not only to be not science[89], but even worse appeared to be surgery not medicine[90]. As will be seen, the attitudes and reactions in Britain were

[84] Cameron 2002, p141: "It is also worth noting the beginnings here of the injurious divide between 'tradesmen' 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, particularly Germany and the United States."

[85] Peitzman 1996, p280: "…the emerging new specialty of nephrology assumed a bipartite form: it comprised, metaphorically, the high-caste tribe of the flame photometer, and the new but proliferating practical-minded tribe of the artificial kidney. They have worked together and learned from each other, though from time to time members of each speak ungenerously of the other."

[86] Welt LG, Peters JP. Acute renal failure: Lower nephron nephrosis. Yale J Biol Med 1951; 24: 220-230: "The value and proper role of the variety of artificial dialyzing procedures remain subject for investigation. Peritoneal lavage carries a serious hazard of infection…It has been convincingly demonstrated by Merrill and his associates and others that an artificial kidney of the Kolff design in competent hands is an efficient and reasonably safe dialyzer. 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."

[87] Peitzman 1996, p301: "Known for his moral fervour concerning both medical and political issues…Peters disdained the seemingly free-wheeling attempts to dialyze patients without a suitable controlled study….Peters' trainees recall that in fact he showed no favourable interest in hemodialysis, rarely talked about it, and did not want it at Yale."

[88] Peitzman 1988, p227: "Nephrology from the 1950s into the 1970s blossomed within academic medicine and advanced more slowly outside it."

[89] Peitzman 1988, p228: "In its natal period, dialysis had seemed to some of the then senior protonephrologists as a dubious flash in the pan, cherished by neophytes. Sometimes dialysis research depended as much on engineering as it did on renal physiology, and its language of discourse became increasingly opaque to other nephrologists…" Peitzman 1997, p303: "…those investigators in Europe and the United States, whom we might now call 'protonephrologists' and who emerged from the metabolic/chemical tradition, did not see work with the artificial kidney as 'science', at least not as they understood their own sophisticated, quantitative work. In their eyes, the artificial kidney was inventing in a basement, exotic pragmatism – not science. And in some countries a lot of the work was carried out by surgeons, not internist-investigators. Eventually, quantitative scientific analysis was applied to many aspects of dialysis, but in its early clinical years, the practice marched ahead of the theory: there was not much science in early hemodialysis. Also, by the early 1950s, careers and reputations were already invested in artificial kidney development, or in electrolyte metabolism work."

[90] Alwall 1986, p53: "The development of active therapy…was delayed, but it did go on in the 1950s in spite of strong opposition, especially of colleagues in internal medicine. It was in surgery that dialysis

comparable to those in the USA. The artificial kidney in the early days seemed to succeed most in surgical settings, and in many places the early users and inventors of dialysis were surgeons, particularly urologists. Alwall later recollected that 'active' measures, such as blood transfusion, were reserved for surgeons; he also suggested that age influenced the pro- and anti-dialysis lobbies[91], and Peitzman also emphasises the 20-year age difference between Thorn and Peters (Peitzman 1996, p278) and suggests that most medical innovations at first attract mainly younger men. This marginalisation of dialysis and its protagonists is sharply emphasised by John Merrill who, although later regarded as having probably done more than anyone to make dialysis respectable, appears not to have enjoyed high status at the Peter Bent Brigham Hospital, at least early on[92], a point indirectly substantiated by Fox's detailed study of the PBBH Metabolic Group (Fox 1998), conducted at the time when dialysis was successfully developing within the group and was receiving much national and international attention, but in which dialysis receives only cursory mention and Merrill none at all. A further contribution to the slow and erratic adoption of dialysis was that the treatment was not overwhelmingly endorsed by those who had actually tried it – a factor that not only fuelled the intellectual opposition but also reassured the empirical majority reluctant to venture into new and uncharted therapeutic territory. Proponents of, and experts in, dialysis such as Merrill were cautious in their advocacy, emphasising the need for holistic management (including 'conservative' treatment)[93], whilst others, who were initially convinced of the utility of dialysis, became sceptical and joined forces with their influential seniors such as Peters and Grollman[94].It is reasonable to conclude that, in the early 1950s, it was by no means inevitable or even likely that dialysis would be accepted. "But a major and unexpected motor of change appeared" (Cameron 2002,

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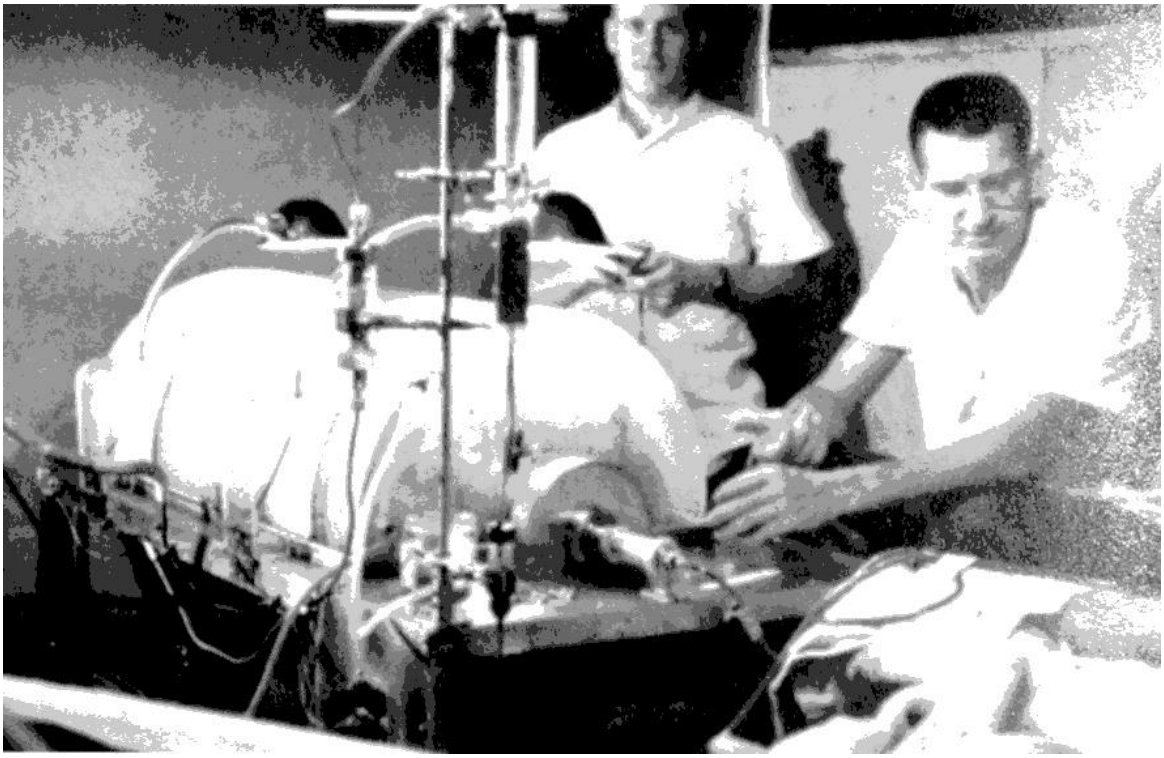
attracted increasing interest." This attitude has been slow to fade: "It has been remarked by many that nephrologists involved in dialysis tend to have the personality and skills of surgeons and not physicians, if such stereotyping is deemed to be possible." (Cameron 2002, p117).

[91] "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."

[92] According to Cameron (2002, p137), when Gabriel Richet visited Boston from the Necker Hospital Paris in 1954, he reported: "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 artificial kidney and his first attempts at renal transplantation."

[93] Merrill (1950): "…it is not possible at the present time to draw definite conclusions as to the efficacy of such a procedure in the general treatment of renal disease."

[94] Fishman AP. Treatment of acute renal insufficiency. J Amer Med Assoc 1949; 139: 473-474. "…it was soon found that despite the urgent transfer [of patients] to the [Mount Sinai] Hospital, mechanical dialysis was not necessary. Under conservative management, diuresis and cure occurred spontaneously."



p138) – the Korean War. "on this occasion, however, the problem was immediately evident rather than retrospectively analyzed" (Cameron 2002, p139): the mortality in anuric casualties was >85%, compared with 5% for all battle casualties. The US Defense Department response was twofold: Paul Doolan (trained at the PBBH) and George Schreiner (who had set up dialysis in Washington after attending Kolff's 1947 New York lecture and demonstration) were sent to investigate the problem, and identified hyperkalaemia due to stored blood and the practice of a pre-battle hearty meal as a major contributory factor to death in uraemia. Secondly, the Army[95]established a dialysis unit at the Walter Reed military hospital in Washington, DC in 1951 and this transferred in April 1952 to the 11th Evacuation Hospital near Pusan, a 30 minute helicopter flight from the forward MASH. This unit was successively directed by Lloyd H Smith and Paul Teschan, both from the PBBH. The results from the Pusan dialysis unit, using the Brigham-Kolff machine, showed a 55% reduction in mortality in anuric casualties (a success rate not achieved since). Teschan and others heartily endorsed the benefit of dialysis both personally[96] and in publications, in which the unexpectedly impressive

[95] Cameron 2002, p177, footnote 29: "…the important role which, almost uniquely in the United States, the military played in the development and use of the artificial kidney." (The Army Department later sponsored Warren E Collins Inc, Boston to refine and supply the MacNeill dialyser for use in the Vietnam War (McBride 1979, p38)).

[96] Letter from PE Teschan, dated 04.11.1952, to Edward A Olsen, the engineer responsible for the Brigham-Kolff machine (reproduced in McBride 1979, p32): "You will be interested to know that the Kidney works as well here in a rice paddy in Korea as it did in Washington, and to a far more constructive purpose; since 11 October we have averaged one dialysis per day, and the patient influx continues. These

results largely silenced the opposition. Dialysis went to Korea an unproven experimental therapy, it returned with its credentials validated: it did work, it did save lives. Dialysis still had a long way to go but had passed the point of no return: acceptance. Within the general civilian context it became less of an audacious oddity as other organ-supporting technologies entered the medical arena[97]. But the Korean War experience did more than apply the imprimatur of success on the machine, it also set the pattern (established by the PBBH group) of how renal failure should be managed in the future: a process involving a team, each individual within which with a specified role, covering the *entire* medical, technical and nursing management of the oliguric patient[98].

2.7 Competing technologies: Peritoneal Dialysis v Haemodialysis

Not only was there little semblance of order in the variety of haemodialysis machines available, there was also a choice of dialysis modalities. It is here that we must divert to the history of peritoneal dialysis, seeking to ascertain how and why, when a *choice* was presented, haemodialysis gained precedence. (The chronology of peritoneal dialysis (PD) in Table 2.7 stops short of its renaissance as Continuous Ambulatory Peritoneal Dialysis (CAPD) for end-stage renal failure from the 1980s onwards). During the early period of dialysis, other modalities were explored of which the most significant were exchange transfusion and intestinal dialysis. None of these methods gained any traction because they were recognised to be not only inefficient in terms of solute removal but also impractical, often unpleasantly so in the case of intestinal dialysis. Two major problems affected the reception of early haemodialysis: the machines were expensive and difficult to use, and repeated vascular access was problematic from the earliest days[99], not to be resolved (and then only partially) until 1960 (Figure 2.12).

Cameron (2002, p95) states:

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are very seriously wounded casualties from the line who have generally been in profound shock and have received massive blood transfusions. Their plasma NPN and potassium levels rise rapidly to dangerous levels, and most require more than one dialysis. Bleeding which might be lethal if heparin were used has not been a problem much to my surprise. In the short time we have been in operation, I am reasonably certain that at least twenty soldiers of the United Nations force owe their survival to the dialyzer."

[97] Peitzman 1996, p280: "The artificial kidney matured as other machines joined it at the bedside…Technological diagnosis and treatment symbolized modern American medicine; using machines became the norm."

[98] Drukker 1989, p34

[99] Cameron 2002, p79: "Already major problems with access were evident…, some of the acute patients who had had repeated dialyses but remained anuric eventually ran out of access and could no longer be treated, an observation that was to be repeated over and over in other settings."

"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."

But a group in New York received a wartime contract from the Navy Department to explore the use of peritoneal lavage in acute uraemia. After extensive methodological and animal studies, Fine and Seligman published their first successful clinical case in

1924	Georg Haas: glass cannulae in radial artery and cubital vein; later cut-down to radial artery and adjacent vein.
1943	Kolff: venepuncture needles in femoral artery and vein; later cut-down to radial artery: severe problems with bleeding (heparin).
1946	Murray: catheters in vena cava (veno-venous dialysis).
1949	Alwall: rubber and glass arteriovenous shunt (clotted).
1960	**Scribner: Teflon shunt.**
1961	S Shaldon (London): Seldinger technique hand-made catheters in femoral artery and vein (repeated use); later veno-venous reduced bleeding after removal.
1966	**Brescia-Cimino arteriovenous fistula**[1].

1. Cameron 2002, p194: "Unlike all other major developments in dialysis, the arteriovenous fistula did not require new materials – only new ideas."

Figure 2.12. Chronology of vascular access

1946, to some critical acclaim[100]. (Despite PD being essentially an American invention, Peitzman, the historian of American nephrology, makes no mention of it – perhaps an indication that PD has for long been regarded as the 'poor relation' of haemodialysis, possibly because of its low-tech status). The introduction and development of PD shows some contrast to HD: it was subjected to some early comparative or even controlled laboratory experiments, it appeared successful, and it was vigorously promoted by some influential established American physicians. As regards success, even allowing for what must have been considerable publication bias, by 1948 there had been reported in English-language journals 101 patients who had been treated by PD, of whom 63 had acute reversible renal failure, and of these 32 (51%) had survived (Odel, Ferris et al. 1950). In contrast, by 1950 haemodialysis had been reported in 110 patients in 13 centres

[100] ED Churchill, 1946, at the meeting of the American Surgical Association, quoted in Drukker 1989, p480: "…despite all the optimistic reports on the successful management of shock in this war, renal shutdown was the stonewall against which we butted our heads many times…The surgeons caring for these patients with anuria tried many forms of treatment: high spinal anesthesia; alkalies to the point of severe alkalosis; and many other measures. Dr Fine's methods represent one more procedure, that may be applicable to men suffering from renal shutdown following severe trauma. I hope it will prove successful…" Note: the general concept of ARF without trauma was still hazy.

in 7 countries, of whom there were 37 survivors (34%)[101] (Merrill 1950). This is in no way to assert that the two collections of cases were necessarily directly comparable, inclusive or rigorously analysed. Indeed they do not deserve consideration as proper series. Nonetheless, they show that the clinical results available at that time suggested that PD was at least as effective as HD, if not rather better. The evidence, such as it was, could not have been construed as indicating the clinical superiority of HD as the dialytic treatment of choice.

Exchange blood transfusion was investigated at the Necker Hospital in Paris between the mid-1940s and the mid-1950s and once or twice in New York (Cameron 2002), but was not widely used as it proved relatively ineffective, was laborious and used large quantities of a scarce resource. At the Hotel Dieu Paris, PD was used successfully from 1947 and was further encouraged after Marcel Legrain visited Merrill in 1951 (Legrain and Merrill 1953; Derot and Legrain 1954). The Necker and other hospitals also performed intestinal dialysis (Maluf 1948; Vermooten and Hare 1948; Maluf 1950), but it was abandoned in favour of PD and HD. The Necker experimented in the laboratory with an Alwall machine in 1952, but found it too difficult to use. They used, and subsequently modified, a Kolff-Brigham machine from November 1954 after Gabriel Richet also visited Merrill in Boston. The very active Paris units (Richet, Crosnier et al. 1954) abandoned alternative therapies in favour of HD, but the reasons for their choice are not recorded. Intestinal dialysis was probably sporadically used in many places, but the absence of more than hints of this in the medical literature suggests that its use was neither widespread nor systematic. It was a rather unpleasant and messy procedure of limited efficacy. Although it could be performed without special equipment, its use had the appearance of desperation in the absence of a viable alternative.

It may well be, however, that this constructs a therapeutic dilemma which did not actually exist in the early 1950s. The choice was not really between the available dialysis techniques, but rather the decisions hinged on more fundamental issues. Primary among these was the question whether dialysis in any of its manifestations had merit over and above the competing dietary ('conservative') management of renal failure, and if so in which clinical circumstances. This contestation had particular resonance in Britain, and

[101] Cameron 2002, p115: "In contrast to the relatively encouraging results with peritoneal dialysis…, 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 almost always used in those already moribund. There was a plethora of patients with irreversible disease, on whose grim outlook dialysis had little or no impact."

is discussed in that chapter. Further, the options included even more basic principles: was renal failure of sufficiently high profile to warrant the attention of a significant segment of the profession, be they general physicians or surgeons? Very few 'artificial kidneys' were in active use worldwide and only a handful of people were interested.

The choice between PD and HD was made twice: definitively in the mid-1950s and rather morphlessly in the late 60s/70s. These later events are discussed in the appropriate sections. Suffice it to say, the drama of the use of the dialysis machine in the Korean War emboldened its enthusiasts and attracted the attention of a wider audience, predominantly composed of those already inclined towards the active management of renal failure. A counterfactual speculation might be about the consequence if the US Army had chosen people performing PD rather than those linked to the (almost unique) PBBH haemodialysis centre, the history of dialysis and of nephrology would have been very different as PD would probably have been less eye-catchingly successful in the highly catabolic severely traumatised wounded. Merrill at PBBH had used and published on the use of PD in ARF, including in septic patients (Legrain and Merrill 1953; Burns, Henderson et al. 1962), but he never spelled out the reasons for abandoning the technique. It was this perceived inadequacy of PD for severely metabolically deranged patients that led to its second rejection in favour of HD some 20 years later. However, at least until the 1980s, it may well have been true that, as Drukker suggests, the choice between HD and PD by individual doctors in specific circumstances depended largely on personal preference and experience, the availability of equipment, and often on contra-indications to either method (Drukker 1989, p489).

PD had all the practical problems of a fledgling technology – equipment and dialysis solutions had to be laboriously concocted on an *ad hoc* basis, there was no agreed satisfactory method of access to the peritoneum, there appeared to be no way to prevent or treat the inevitable iatrogenic intraperitoneal infections. Much changed in 1959 when Baxter/Travenol entered the field, supplying PD fluid in bottles, PVC tubing, and a catheter for acute access to the peritoneum. Thereafter PD became standardised and relatively easy to perform (Cameron 2002, p144). Even the British medical press, which had been consistently hostile towards dialysis, gave lukewarm approval to PD[102].

[102] "Peritoneal dialysis is obviously no 'silver bullet' for renal failure, but in suitable cases it is a good leaden bullet, which should perhaps be more commonly fired." Anon (1959). "Intermittent peritoneal lavage." Lancet **2**: 551-552.

Enter on the scene Arthur Grollman, distinguished professor of medicine in Dallas, Texas. His highly influential book (Grollman 1954) lucidly summarised the clinical syndrome of ARF, disparaged previous therapy ("misguided and resulted in harm"), and firmly endorsed the conservative management of ARF[103]. Grollman was among the powerful conservative lobby resisting the advent of the artificial kidney but, unlike others, offered an alternative: peritoneal dialysis, which he advocated "…because of its easy and general practicability" (p54)[104]. He not only gave detailed instructions for the procedure, but also travelled far and wide to insert PD tubes. In the UK, a surgeon at Colchester was among the first in the world to treat patients with PD (Reid, Penfold et al. 1947; Reid 1948). According to Cameron, during the 1940s PD was in widespread use, especially in the USA, but there were only single or a handful of patients at any centre, and most probably gave up because of difficulties and lack of success.

There was no consensus of opinion on preferred treatment or even any treatment at all[105] and even those closely involved in dialysis were, at least at times, ambivalent. One factor in the lack of widespread acceptance of either form of dialysis was confusion about when or if it should be employed, and how. Cameron 2002, p116:

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

Despite the dilemma over the most efficacious mode of treatment, there has never been any rigorous assessment of management[106]. This absence of evaluation is not unique to nephrology. In some cases, for example dialysis and pacemakers, the

[103] Grollman 1954, p39: "…use of artificial measures as temporary expedients." "Only in a small percentage of patients and in those who have been mismanaged or in whom complications supervene, is it necessary to resort to the use of artificial measures…"

[104] Grollman 1954, pp 57-58: "The use of the artificial kidney is limited to the relatively few institutions where a well-trained team acquainted with its manipulation is available. It is too expensive and complicated for general application, particularly since a simple method (peritoneal lavage) requiring no special and expensive apparatus and which is more easily applied and equally effective is available for clinical use. Although simple in principle, many factors complicate the use of the artificial kidney…These all mitigate against its use in the infrequent occasions when some extrarenal device is needed…"

[105] Cameron 2002, pp113-114: "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 that time, and it is instructive to note that…Kolff himself explored all of these techniques as did…Alwall…Claus Brun and Jean Hamburger. There was no *clear* message as to what would prove the best treatment in the long run, or whether there were any improved outcomes…"

[106] Cameron 2002, p205: "It is interesting…that there was remarkably little debate, and no controlled studies, comparing peritoneal dialysis and haemodialysis…either then or since."

innovation was introduced and accepted into mainstream practice many years before the concept of formal assessment had impinged on the collective medical consciousness. Nevertheless, it is the thrust of McKinlay's argument that assessment frequently only occurs after an innovation has been adopted by the profession and institutions, and endorsed and supported by the state and/or underwritten by third-parties[107]. But McKinlay fails to provide convincing examples of where wrong decisions were made and persisted with. By the time of this acceptance, the innovation has received professional and public approval based on uncritical opinion rather than solid fact. "Once social policy is implemented, the career of the innovation can be regarded as having passed the point of no return. " (McKinlay 1981, pp386-387). It becomes increasingly difficult to perform proper scientific evaluation once a procedure has become established as 'standard' and reputations and resources have been irrevocably invested. McKinlay, and others, further argue that the establishment and maintenance of a procedure is a social process dependent on the power of the sponsors[108]. Nephrology provides a case in point in support of this thesis, which may also cast some light on how HD became the dominant treatment modality for ARF. In the 1980s, CAPD was developed in the USA but only widely adopted in the UK and parts of Europe. It is an effective, cheaper alternative for some ESRD patients, and does not require capital outlay on infrastructure. In the USA, where institutions had invested heavily in HD facilities, which were largely run by for-profit organisations, the take-up of CAPD was tiny, but in the chronically underfunded UK up to 80% patients were treated in this way in some units. In the USA, there was financial incentive to oppose the 'new' treatment; in the UK the financial pressure resulted in over-adoption (Stanton 1999).

2.8 Why dialyse at all?

As has been previously noted, those involved in the invention and adoption of dialysis later averred that they were motivated by a sense of inadequacy and frustration when

[107] McKinlay 1981, p387: "The defective empirical foundation of the state's endorsement of an innovation is manifest in the research and development that the state subsequently funds. Having taken the step of endorsing…the state…seeks to determine whether in fact it was the correct step to take. A careful review of the early careers of many different innovations reveals that, more often than not, the step was in quite the wrong direction and wasted resources, diverted professional resources to unproductive activities, and misled the public."

[108] McKinlay 1981, p398: "It is reasonable then to argue that the success of an innovation has little to do with its intrinsic worth (whether it is measurably effective, as determined by controlled experimentation) but is dependent on the power of the interests that sponsor and maintain it, despite the absence or inadequacy of empirical support. The power of such interests is also evident in their ability to impede the development of alternative practices (for which there may also be considerable observational support) that could conceivably threaten an activity in which there is already considerable investment."

faced with terminal renal failure for which they were therapeutically impotent. Without exception they cited specific memorable cases, individual patients who for some reason imprinted themselves on the clinician's psyche. Kolff, Alwall and Thorn were revered within the profession for their integrity, among other qualities. It must therefore be accepted that, notwithstanding any retrospective refinement, that this imperative to do 'something' drove not only these individuals, but also most physicians. Thus we might invoke an emotional compulsion stimulating the first colonists within a field, who proselytise colleagues and the public. These come to share this unquestioned obligation, a real need, to uncritically apply a new technology even before it has received the imprimatur of formal bureaucratic assessment and approval.

It is undoubtedly the case that "…conclusive evidence for the life-saving ability of the artificial kidney was far from abundant in its first decade of use" (Peitzman 1996, pp278-279) and "despite local enthusiasm, it was far from clear in its early years that the artificial kidney actually *did* save lives (Peitzman 1997, p301). Why then did an increasing number of those interested in kidney disease adopt dialysis? At least part of the answer is provided by Koenig's[109] technological imperative (Koenig 1988) and Warner's desperation-reaction mode of diffusion of innovation (Warner 1975). The essence of the therapeutic dilemma and the medical reaction to it has been well captured by Peitzman (himself a nephrologist turned historian) (Peitzman 1997, p302):

> "…only a clinical sense of *desperation* can justify and stimulate development of a complex, potentially hazardous medical innovation. If a patient is truly near death, less objection arises to trying a new therapy, even one that is only half developed."

A logical dilemma arose from the conjunction of ARF, with its potential for recovery, and the dialysis machine, with its potential for keeping the patient alive long enough for that recovery to take place. Controlled comparison studies of ARF with and without dialysis might have solved this conundrum, but such studies were never contemplated or performed. The dilemma hinges on making a balanced evaluation of the role of dialysis. If a patient is dialysed but dies, then the machine did not help, at least not enough. But the failure of dialysis may be due to the patient's condition and disease process or to delayed or insufficient treatment. Thus failure may be an expression of the inherent

[109] The widely used phrase 'technological imperative' was coined by health economist VR Fuchs, who suggested that physicians are 'imprinted' during training to provide the best possible medical care, which is generally interpreted as the newest and most technological care. Fuchs, V. R. (1968). "The growing demand for medical care." New Engl J Med **279**: 190-195. This is perhaps a slightly different emphasis from that adopted by later commentators.

inadequacies of the device, or of the hopelessness of the clinical condition. However, if the dialysed patient recovered, there was no certain way to attribute success to the machine. This dilemma was recognised early by Isidore Snapper (Snapper 1949) and continued to generate contention for several years. The ambiguity could accommodate diverse opinion: those opposed to mechanical intervention could reasonably regard it as unproven and superfluous, and its enthusiasts could equally reasonably see it as an essential progression beyond the current therapy. Peitzman (2001, p200) explores this further:

> "…eventually a medical community may conclude (sometimes wrongly) that a novel treatment is effective…For the artificial kidney, investment in hardware and staffing may be sizeable, as the new treatment finds its 'presence' in the hospital. Use of the treatment begets more use: the device is there, attended by trained retainers who want to use it and ought to be kept busy. The new modality is up to date and believed to help those treated with it, at least sometimes. How can it not be offered to patients suffering the ailments it corrects? This shared sense of obligation has been referred to as 'technological imperative'."

To the variety of social and economic determinants of the acceptance of a new technology is added an ethical mandate to deploy any and all measures that might conceivably benefit the patient. In this regard, the interests of the physician and patient may converge. The particular emotive social context of dialysis and transplantation has received much attention (Stanton 1999; Stanton 2000; Fox and Swazey 2002; Stanton 2005) and in each case "the idea of a technologic imperative is both powerful and captivating" (Koenig 1988, p466), that is to say:

> "…once a new technology is developed, the forces favoring its adoption and continued use as a standard therapy are formidable...Especially in the case of medical technology, with its potential for evoking strong feelings carrying potent symbolic references to the body, life, and death, the relationship between the machine as object and its user is multifaceted." (Koenig 1988, p467)

Stanton has shown the life-supporting technologies, most particularly dialysis, are those in which the moral imperative for their use is most forcibly demonstrated (Stanton

2000)[110] and which are the focus for what Fox and Swazey call the experiment-therapy dilemma (2002, pp60-83)[111].

Fox and Swazey posited a continuum between [laboratory] experimentation and established therapy for which there are no agreed indicators of where in the continuum an innovation may stand at any given time. This uncertainty results in part from the ambivalence of the dual role of doctors as both investigators and therapists. Doctors may consequently be caught in an intellectual dilemma which Fox and Swazey characterise as an emotional balance between investigative [experimental] zeal and clinical fervour. The latter could potentially lead to an optimistic overestimation of the therapeutic value of a treatment or, depending on the circumstances and characters involved, over-cautious resistance to innovation. They suggest that the experiment-therapy dilemma arises from the absence of detailed criteria for making at least three critical decisions:

- How to tell whether laboratory work has sufficiently solved the conceptual, empirical and technical problems presented by the therapeutic innovation;
- How to determine whether results of clinical trials [experiments] justify continued use;
- What results definitely indicate, on both scientific and ethical grounds, that a new treatment may be used on patients who are not terminally ill? This leads to a "statistical morality" in which mathematical decisions may decide what is an acceptable mortality from procedures if the condition carries an overwhelming death rate.

Fox and Swazey's views are particularly apposite as they draw their evidence from American organ transplantation, artificial hearts and dialysis (Fox and Swazey 1992; Fox and Swazey 2002). The time-bound nature of their studies (most evidence comes from pre-1970) is relevant to the early days of dialysis and transplantation and hence relevant to the present work. There should be a possible note of caution in generalising their conclusions as they are based on a period when formal ethical procedures did not exist and even informal ethical concerns seem to be absent. An important facet of Fox's publications is the close observation of the renal programme at PBBH (Fox and Swazey

[110] "the histories of the iron lung…and the kidney dialysis machine…illustrate the allure of what we might call the resurrectionist capacity of technology." Rothman, D. J. (1997). Beginnings Count: The Technological Imperative in American Health Care. Oxford, Oxford University Press.

[111] Fox and Swazey's investigation relates largely to the origins of kidney transplantation at the PBBH and, in particular, the attitudes and actions of FD Moore, the Surgeon-in-Chief.

1992; Fox 1998; Fox and Swazey 2002). There is focus on FD Moore who was Surgeon-in-Chief during the period of the early transplant programme, perhaps because he so well exemplifies their experiment-therapy dilemma. Thus Moore in later publications (Moore 1965; Moore 1968) justifies the risks [to the patient] of experimental clinical transplantation on the "expectation" that "all the techniques of modern medicine and surgery" would be successful. In fact, the results were dreadful: less than 10% of recipients survived more than three months. A procedure with a mortality comparable to that of the underlying condition would have defied statistical justification, had the investigators applied any objective analysis. It would appear that Fox and Swazey's critical decisions were, at least in the 1950s and 60s, based not on 'detailed indicators' but on individual observers' assessment. This is, of course, relevant to the introduction of a number of technologies at that time, including dialysis.

Koenig explains the resolution of this dilemma thus:

> "Once a machine is in use, even if in a limited way, it is very difficult to change course and stop using the machine; its use becomes entrenched." (p487)
>
> "The technological imperative is sustained by inherently social forces which result in a new meaning…: the meaning of standard therapy." (p485)

She goes on to ask, and answer, the question that drives the protagonists of life-saving or life-supporting therapies (pp485-486):

> "…how does the technological imperative become transformed into a moral imperative to provide a new therapy? The notion of an imperative implies constrained choice…The moral tone derives from the sense of social certainty experienced by health professionals. The standard of care becomes a moral, as well as a technical, obligation…When a therapy clearly belongs in the experimental camp…there is no obligation to provide it. Yet when a new procedure has crossed over the mysterious boundary into the territory of standard therapy, it cannot be denied…Once a new therapy is available it becomes extremely difficult, if not impossible, to forego its use."

Stuart Blume has also explored the circumstances in which specialists may be said to manipulate the acceptance of their particular innovations and how, once the innovation is introduced, it proves difficult to challenge or even modify the new actuality. Drawing examples from a range of medical disciplines (Blume 1974; Blume 1992; Blume 1994; Blume 2000; Blume 2006), he considers the interplay between the weight of evidence or argument and the forum in which decisions on the continued adoption of an innovation

are reached. Blume's arguments resonate with aspects of the uptake and persistent dominance of the kidney machine. Different medical constituencies are influenced by different sorts of data: doctors espouse individualised case-based evidence; the decisions of bureaucracies and public health officials are ideally based on statistical data. Yet seemingly objective statistics are frequently trumped by the specialists' advocacy based on the emotively powerful argument of empirical experience. Cumulative empirical advocacy results in institutional 'lock-in' or 'path-dependency'. Once an institution has taken ownership of an innovation the investment in time, people and resources makes it increasingly difficult to reverse or curtail the use of this technology. Further, a range of pressures (medical advocacy, institutional competition, uncritical public and media enthusiasm) persuade other organisations to likewise adopt the technology or practice.

From the late-1950s, haemodialysis did not have to prove itself. A post-war generation of doctors and the public believed that science as manifest in technology was the way forward, and therefore any innovation was more than acceptable, it was desired as necessary. Its use was ethically and morally mandated. The empiricism of its supporters could not be challenged by statistical analysis, which simply did not exist. It was no longer the proponents of the machine, but rather the opponents, who had to prove or disprove its worth. Opposition, or even reasoned questioning, became increasingly difficult as take-up accelerated after the initial adoption by influential centres.

There is a further more subtle force which tends to move an innovation from experimental to established status. Blume has shown that specialties impose their own evidential end-points and methods of collecting and evaluating data. These predetermined criteria derive from their own practices and conventions, thereby excluding alternative or additional ways of appraisal. Ethical or economic evaluations had little or no role in the original acceptance process for dialysis. Much later, as renal support became incorporated into intensive care, the issues of ethics, cost-benefit, and who controls the data became increasingly relevant and contentious. But by then, as Blume points out in a different context (Blume 2006), the transnational harmonisation and standardisation of medical science had increased expert consensus, which serves the interests of both medical scientists and industry. The "universalistic and rationalistic aspirations" of scientific medicine ensured that the possibility of shifting the utility debate to any sufficiently authoritative alternative jurisdiction (economics or ethics) was severely limited. Once established, and that establishment may result from the absence of persuasive negative contention, a technological innovation achieves its own

momentum. It becomes the new *status quo* maintained by social and professional interests and only challengeable by a replacement technical paradigm, at which point the cycle restarts.

These arguments give the machine, or other medical innovation, centrality – if it was not there, the dilemma would not exist. There are at least two interested parties in the medical encounter. The causality dilemma – how to assess in an individual case whether or not an intervention was, might have been under different circumstances, or could be beneficial – is not device-specific, it is dependent upon the attitudes of the participants and these attitudes and behaviours are pre-formed. Practitioners are, as a consequence of inherent behaviours nurtured by a pattern of education, inclined or even committed to intervention. For the patient, and the public, the 'do nothing' option is the least attractive of available choices: uncertainty about the personal advantage of an intervention is preferable to the perceived certainty of the outcome of non-active treatment. It matters not whether this certainty is based on fact, the medical attendant's opinion, or the unspoken or unformed fears of the patient; it remains to that individual a certainty. This must have been the basis of the medical encounter throughout history, the justification for the population seeking and accepting what was offered as the best available treatment. In the Western tradition, the demand, the need, for treatment legitimised mercury for syphilis, camphor for cholera, bloodletting for all ills. If the patient and the public believe that science and technology hold the answers, as they came to do in the post-war period, they then seek a technological solution to their ailments. The moral imperative then arises from within and without the physician. When a new or experimental therapy is presented to a situation for which no useful alternative exists, all the participants have an interest in its application. As Marks indicates (Marks 1993), "The vast majority of decisions to use medical technologies are still made at the bedside, by physicians using conventional medical (and social) criteria." (p1604). That is, the physician *chooses* to provide a therapy but his choice is increasingly constrained as a therapy is promoted and accepted. However, the ethical obligation which physicians perceive to override treatment choices also allows them to assume the moral high ground, reflected in the statements of the early advocates of dialysis[112].

[112] From the Panel Discussion at the American Society of Artificial Internal Organs meeting 1956 (Trans ASAIO 1956; 2: 132, 136):
George Schreiner: "…all of us are considerably nauseated at having people say, 'Well I once had a patient who went anuric for six weeks, and recovered. Therefore there's no reason for treating a patient who has only been anuric for 12 days', even though this patient is dying in front of you of uremia."

The early career of dialysis has been summarised by Peitzman (1997, p303) as driven initially by clinical desperation and the appeal of the idea to some technologically-minded clinicians. It was opposed by economic and practical constraints, but not by ethical questions. The attitudes of a scientific elite slowed its adoption, in part because the established opinion-formers identified its unimpressive early results and could offer an alternative non-invasive therapy based on accepted physiological thinking. Support for dialysis slowly gained momentum so that by the mid-1950s its proponents had garnered sufficient evidence to satisfy themselves of its efficacy. This was enough to push dialysis across the "mysterious boundary" between experiment and established therapy. This career provides a model for medical historians interested in the development of technology and specialisation, the creation of opinions and practices – particularly those who may be interested in exploring exceptions to assumed rules.

Dr Danzig: "…the reason we don't dialyze patients earlier in acute renal failure is because of an opposition that we've had by non-dialyzers, and not because of anything we believe ourselves."

TABLE 2.1 . EARLY HAEMODIALYSIS IN HUMANS

(from Cameron, 2002 pp 121 - 122)

Investigators	**Date**	**Type of Dialyser**	**Place**
Georg Haas	Feb 1925	Collodion, own design	Giessen, Germany
Wilhelm Kolff	March 1943	Rotating drum, own design	Kampen, Netherlands
Rhoads & Saltonstall	Spring 1944	Static coil, own design	Philadelphia, USA
Nils Alwall	June 1946	Static coil, own design	Lund, Sweden
Eric Bywaters & Mark Joekes	Sept 1946	Kolff	London, UK
Gordon Murray	Oct 1946	Static coil, own design	Toronto, Canada
Michael Darmady	Early 1947	Modified Kolff	Portsmouth, UK
Conrad Lam & Joseph Ponka	1947	Murray coil	Detroit, USA
Russell Palmer	Sept 1947	Kolff	Vancouver, Canada
Enneking & Geelen	Early 1947	Kolff	Nijmegen, Netherlands
Maurice Derot	1947	Formalinised intestine	Paris, France
Isidore Snapper	Jan 1948	Kolff	New York, USA
Nannie de Leeuw	Feb 1948	Kolff	Montreal, Canada
John Merrill & John Thorn	June 1948	Kolff	Boston, USA
Kurt Steinitz	1948	Alwall coil	Haifa, Israel
J van Noordwijk & JS Brien	May 1949	Kolff	London, Ontario, Canada
Leonard Skeggs & Jack Leonards	May 1949	Flat plate, own design	Cleveland, USA
Tito de Ribeira	May 1949	Murray coil	Sao Paulo, Brazil
Bodo von Garrelts	Aug 1949	Static coil, own design	Stockholm, Sweden
Maurice Derot	Oct 1949	Kolff	Paris, France
Sterling & Doane	1949	Flat plate, own design	New York, USA
?	Oct 1949	Allis-Chalmers (Kolff)	Milwaukee, USA
?	1949	Flat plate (Kolff)	Leiden, Netherlands
Rosenak	1949/50	‘Flat-coil’, own design	New York, USA

TABLE 2.2. CHRONOLOGY – EXTRACORPOREAL CIRCUITS

1889 BW Richardson (London) and others dialysed in vitro either defibrinated whole blood or serum.

1913 Abel JJ, Rowntree LG, Turner, BB. On the removal of diffusible substances from the circulating blood by dialysis. Trans Assoc Am Physicians 1913; 58: 51 – 54.

John Jacob Abel (1857 – 1938), Professor of pharmacology at Johns Hopkins, Baltimore – many achievements including the crystallisation of insulin; Leonard George Rowntree (1883 – 1959), physician – also invented the phenosulphthalein test (with JT Geraghty in 1910 and 1912), first measurement of blood volume by dye-dilution method (1915), introduction of iodine to X-ray the renal tract (1923), described the histology of lupus nephritis (1922); Benjamin Bernard Turner, English biochemist who made the delicate glass manifold essential for the vividiffusion apparatus. It is almost certain that Abel did not envisage treatment of uraemia by 'vividiffusion', which he used to make 'artificial urine' for laboratory study, but he did suggest that it could be used to remove toxins such as salicylate. (Parascandola 1982; George 1998)

1913 Abel demonstrated removal of salicylate from blood of living animals at a medical conference in London: The Times Monday 11th August 1913: an anonymous article entitled "An Artificial Kidney": '…it is possible that the principle may ultimately be adopted in the treatment of disease.' In the BMJ, the apparatus was described as an 'artificial glomerulus'. New York World 31st December 1913: "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"'.

Most dogs died because of reaction to hirudin, which became unavailable after USA entered WWI, as the leeches came from Europe and were therefore of "enemy origin". In reality, Abel was defeated by the toxicity of hirudin (Marshall 1915).But Abel does not mention use of dialysis for renal failure until the 1920s and 1930s, i.e. after the work of Haas and Necheles. He is reputed to have said that he was unable to help with a case of acute renal failure in 1924.

1914 CL von Hess, H McGuigan: dialysed sugar from blood and realised the importance of agitating or counter-current dialysis.

1915 Alice Rhoad: *in vivo* dialysis to quantify ammonia in blood

1923 Heinrich Necheles (1897 – 1979), Hamburg, constructed a "flatbed" dialyser using goldbeaters's skin and used it on uraemic dogs 'in order to reduce the substances remaining in the body in the case of uraemia which are increasingly poisonous.'

1926-8 Necheles and RKS Lim (Peking): dialysis in dogs with heparin for physiological extracts.

1927 Rowntree and T Shionoya (Mayo Clinic): dialysis in dogs using collodion and heparin: importance of blood turbulence to avoid clotting.

1937-9 William Thalheimer (1884 – 1961), New York: Visking tubing and heparin to dialyse dogs.

TABLE 2.3. CHRONOLOGY OF DIALYSIS SCIENCE

Rene Henri Joachim Dutrochet (1776 – 1847): concept of osmosis.
Thomas Graham (1805 – 1869):

- law of diffusion of gases (1846 and 1849)
- nature of osmotic force (1854)
- redefined "dialysis" – separation of substances across membranes (1861)
- defined "crystalloids", "colloids", "semi-permeable" membranes
- 1854 "chemical osmose appears to be an agency particularly well adapted to take part in the animal economy." "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." Used writing paper impregnated with starch.

Cameron (2002, p27) 'Crucial in determining that in the future investigators would think of using dialysis for uraemia.'
Graham T. Liquid diffusion applied to analysis. Phil Trans Roy Soc Lond 1861; 151: 183-224

1848 Collodion (Paracelsus: substances like glue) synthesised by Carl Friedrich Schonbein (1799-1868)
1850s Adolf Fick (1829-1901) examined diffusion through collodion sheets
1860 W Schumacher: "membrane diffusion": collodion tubes and bags
1907 Lawrence Bigelow & Adelaide Gemberling: comparison of membranes – goldbeaters' skin (lamb or calf parietal peritoneum) best but collodion most practical membrane for dialysis. Analysed diffusion properties in detail – paper must have been known to those attempting *in vivo* dialysis.

TABLE 2.4.CHRONOLOGY OF URAEMIA

Galen (129 – 216 CE): "…thus it is that urine is secreted from the blood by the kidneys and passes thence through the ureters to the bladder, from which it is discharged at a suitable time when reason gives the command." (On the Usefulness of the Parts. Book 2, para 169 – 175).

Hermann Boerhaave (1668 – 1738): post-mortem on a lawyer with urinary obstruction: "…a liquid resembling urine was found in the ventricles of the brain." Also described a 'soapy' substance in the urine (urea).

Andreas Vesalius (1514 – 1564) and Albrecht von Haller (1708 – 1777) removed kidneys and ligated ureters of animals. Haller noted 'vomitus urinosus' in the animals before they died.

Rouelle de Cadet (1718 – 1779) (Paris): soapy substance in the urine.

Antoine Fourcroy (1755 – 1809) and Nicolas Vanquelin (1763 – 1829) between 1797 and 1808 analysed urine and stones – crystallised 'uree'. Suggested: "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 wich is necessary to it." "…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." (Fourcroy AF, Vanquelin N. Nouvelles experiences sur l'uree. Ann Mus Histoire Naturelle 1808; 11: 226)

1821 Vanquelin and Segalas d'Etchepare injected urea: not toxic, only diuresis.

1821 Jean Louis Prevost (1790 – 1850) and Jean Baptiste Dumas (1800 – 1884): nephrectomised animals: urea progressively increased until death.

1827 Richard Bright (1789-1858): seminal clinico-pathological correlation of renal failure and autopsy appearance of kidneys ("granulated kidney").

1827 John Bostock (1773 – 1846) and William Prout (1785 – 1850) independently demonstrated urea in blood of patients with granular kidneys – may have been preceded by Benjamin Guy Babington (1794 – 1866) – all at Guy's Hospital, London.

1828 Rene Henri Joachim Dutrochet (1776 – 1747): proposed urine filtered by kidney

1833 George Owen Rees (1813 – 1889), also at Guy's, showed that at post mortem urea was present throughout the bodily fluids. GO Rees. On the presence of urea in the blood. Lond Med Gaz 1833; 12: 676, 703, 765, 863. GO Rees. Observations on the blood with reference to its peculiar condition in Bright's disease. Guy's Hosp Rep 1843; 1: 317-330.

1839 Robert Christison (1797 – 1882) (Edinburgh): "…ultimately its [granular kidneys] 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." (First description of the anaemia of chronic renal failure).

1839 Addison T. On the disorders of the brain connected with diseased kidneys. Guy's Hosp Rep 1839; 4: 1-9

Pierre Piorry (1794 – 1879): 1840 "contamination du sang par l'urine"; 1847 designated the state "uremie".

1842 Carl Ludwig described filtration through glomeruli

1856 Joseph Picard (1834 – 1896): urea extracted by the kidneys; concentration of urea in renal vein 60% that of the renal artery.

Clinical chemistry was generally disregarded as did not contribute to clinical practice: "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." Graves R. 1848 Clinical Medicine Vol I, p25. Fannin, Dublin

1865 William Roberts (Manchester) suggested that nitrogenous substances "intermediate between urea and albumin" were the cause of uraemic symptoms. (First suggestion of what became known as the 'middle molecule hypothesis').

1898 – 1902 Hermann Strauss (1866 – 1944) introduced hollow needle for *withdrawing* blood (see Cameron 2002, p23 footnote 28, for discussion).

1870s and 1880s Victor-Timothee Felz (1835 – 1893) and Charles Ritter (1837 – 1884) showed the role of potassium in renal death: "…the true agents of the intoxication are almost always potassium salts which accumulate in the blood".

1887 von Jaksch discovered acidosis.

1918 Franz Volhard (1872 – 1950): hypertensive encephalopathy
Volhard and Fahr: malignant nephrosclerosis (MacMahon 1966)

TABLE 2.5. MAIN TYPES OF DIALYSERS/DIALYSIS SYTEMS 1943 – 1966

(from Cameron 2002 pp 158 – 160)

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

1944 Rhoads-Saltonstall
1946 Alwall (in canister)
1946 Murray (open)
1950 Jernstedt-Westinghouse (in canister)
1950 Moeller (in canister, grooved to allow counter-current flow)
1953 Battezzati-Taddei
1956 Dogliotti- Battezzati-Taddei (double, grooved)
1956 Inou
1960 Gal-Nemeth
1966 Rotellar 'glomerulus'

Flat Spiral Dialysers (radial dialysate flow)

1952 Bianchi-Borgi
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 Nose
1962 Lawson-Blainey-Simpson (integral plastic container) †
1966 Hoeltzenbein
1967 Patel-Levy

Parallel Flow Dialysers

Sheet

1949 Skeggs-Leonard
1951 Lowsley-Kirwin
1951 Sterling-Doane-Hollander
1952 Kimoto-Shibusawa-Tango
1953 Murray-Roschlau-Halstrup
1954 Caporale-Pironti
1960 Kiil (and various subsequent modifications, eg Collins 1959)

1961 Niechal
1961 Ananjev
1962 Galletti (‘Klung’ oxygenator-dialyser)
1963 Esmond (‘Dialung’ oxygenator-dialyser)

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 Dialysers

1957 Kuhn
1960 Savino
1961 Zosin
1963 Longmore †

Hollow-fibre Capillary Dialysers

1964 Stewart-Mahon

Reversed Dialysers (dialysate in tubing surrounded by blood)

1952 Guarino-Guarino
1964 Smith-Gara

Fractional Dialysis (dialysis cells)

1950 Bartrina
1956 Bartrina-Nemeth-Gal
1957 Sorrentino (+ electrodialysis)*

* Not used clinically
†United Kingdom

TABLE 2.6. EXPORT OF BRIGHAM-KOLFF ARTIFICIAL KIDNEYS

(modified from McBride (1979), p24)

DATE SHIPPED	
15.07.54	Zurich
4.10.54	Paris
1.02.55	Venezuela *
15.02.55	Buenos Aires *
9.05.55	Paris *
1.12.55	Tokyo
7.02.56	Brussels
??	Rio de Janeiro
5.03.56	Rio de Janeiro
2.08.56	Leeds
16.10.56	Antwerp
1.11.56	Sao Paulo
26.03.57	Montevideo
10.05.57	Uruguay
17.05.57	Verona
30.10.57	Mexico City
9.01.58	Santiago
26.05.59	Buenos Aires *
16.07.60	Naples
21.09.60	Trieste
22.12.60	Sao Paulo *
27.11.62	Costa Rica *

* No specified hospital (government departments or agents).

TABLE 2.7 PERITONEAL DIALYSIS CHRONOLOGY

(Boen 1985; Drukker 1989; Cameron 2002)

1744 Christopher Warwick & Stephen Hales: treatment of recurrent ascites with trocars & instillation of wine (Hales 1744-1745; Warwick 1744-1745)
1833 GO Rees: urea in blood = peritoneal fluid
1862 Friedrich von Recklinghausen (1833-1910): anatomy, histology & physiology of peritoneum
1877 G Wegner: perfused peritoneum of animals, studies of temperature & tonicity
1894 EH Starling (1866-1927): absorption of fluid from peritoneum & demonstrated bidirectional movement of molecules
1902 R Klapp: most absorption via blood vessels
1916 Max Rosenberg: urea in blood = peritoneal fluid
1918 KD Blackfan (1885-1941) & KF Maxey: intraperitoneal administration of saline to dehydrated children; reported that treatment was routine at St Bartholomew's Hospital (Archbold Garrod (1857-1936))
1921 AJ Clark: effect of hypertonic dextrose
1923 TJ Putnam (1894-1975): living peritoneum as dialysing membrane (Putnam 1923)
1923 G Ganter (1884-1940): intermittent PD in uraemic animals; 2 patients with transient benefit (also pleural exchange in 1918)
1924 H Necheles: unable to reproduce Ganter's results
1925 M Landsberg & H Gnoinski: PD uraemic animals
1927 H Heusser & H Werder: unsuccessful continuous PD in 3 patients with mercuric chloride ARF
1931 S Bliss: long-term (~16 days) PD in dogs
1932 E von Haam & A Fine: reversible ARF in rabbits ($HgCl_2$): 8/9 controls died in 3-4 days, 4/6 treated with PD recovered
1934 J Balazs & S Rosenak: unsuccessful PD in 3 patients with ARF (died after 5-7 days)
1938 JB Wear: longer dialysis in 5 patients – 1 improved enough for calculus surgery
1938 JE Rhoads (1907-2002): repeated PD in 2 patients with CRF
1946 H Frank, A Seligman, J Fine: extensive animal experiments; successful PD in patient with sulphathiazol ARF
1946 R Reid (Colchester): 1 successful patient
1946-9 P Tanret & M Derot (Paris): 64 patients with ARF:

	n	died
PD Alone	7	2
No specific treatment	9	1
Exchange transfusion	17	7
PD + Exchange	31	10

1947 H Odel & P Shea: 8/15 survivors
1948 HM Odel; reported 17 survivors
1948 PSM Kop & W Kolff: 21 patients: 5 with ARF: 3 survivors
1948 101 patients in English-language papers: 63 with ARF: 32 survivors
1949 J Schneierson: PD for cardiac failure
1950 E Benhamon: PD for cardiac failure
1951 A Grollman: intermittent PD
1959 M Maxwell: commercial PD solutions
1959 P Doolan: acute catheter – treated patient with CRF for 6 months
1962 next British publication on PD; Miller (urologist) treated 45 patients from 1947
1965 Trocath

3. FRAMING THE CONCEPT OF ACUTE RENAL FAILURE

"Those who suffer from anuria…die within seven days unless a sufficient flow of urine is re-established." (Hippocrates of Cos, Aphorisms VI.44) (Lloyd 1978)

"Wrestling, I will not let thee go, Till I thy name, thy nature know."

Charles Wesley (1707 – 1788), 1742.

"To the clinician it is essential; he cannot live, cannot speak, cannot act without the concept of morbid categories." Knud Faber. 1930, p211.

3.1 Introduction

3.1a Acute Renal Failure: a working definition

Acute renal failure (ARF) is a phrase well-recognised in clinical practice as a significant, life-threatening, complex disorder. Yet, unlike most modern diseases, it lacks a neat, closed definition. It came to be an accepted medical term through a combination of circumstance, symptoms and laboratory readings. As its definition hinges on a disorder of kidney function, and understanding of this dysfunction and its consequences has changed, this definition also has shifted over time perhaps more and more rapidly than for almost any other disorder.

To aid the discussion in this chapter, a working definition of the category of illness called ARF is offered. This definition is not immutable and is time- and circumstance-dependent. Nevertheless it allows both a backward glance at what preceded the mid-20th century adoption of the term, and also a forward look at the unrolling thought patterns which came to define ARF in the changing biomedical world of the late 20th century (further explored in Chapter 8).

ARF is a more or less sudden decline in previously normal kidney function, usually following an identifiable significant clinical event. It often, but not invariably, causes a marked diminution in urine output and always results in marked derangement of blood biochemistry. In all but its mildest manifestations, ARF invariably results in life-threatening critical illness. The kidneys have remarkable powers of regeneration, so that should the patient survive the acute episode there is a reasonable expectation of a return to normality. However, in the absence of medical support, only a small minority of patients actually survive long enough to allow recovery of renal function: the mortality of established oliguric ARF approaches 100%.

Thus, an accepted and acceptable clinical definition of ARF could be: a rapid (hours to weeks) deterioration of kidney function associated with accumulation of nitrogenous

waste products such as urea and creatinine. Oliguria (urine output <400 mls/day) or anuria frequently occur, but are not invariable. It is a clinical syndrome that may be caused by many renal and extrarenal diseases. In this respect it shares features with what are now regarded as 'symptoms', such as fever, which have enjoyed different meanings in lay and professional and in historic and contemporary comprehensions.

3.1b An approach to nosology

Much of the extensive scholarly work on diseases and their classification follows the original thinking of Ludwig Fleck in the 1920s who argued that diseases are idealised pictures of real-life pathological phenomena. But, as Lowy points out (Lowy 2011), the reductive and analytic process by which diseases are defined is imperfect because it is often difficult to incorporate all the pathological and individual manifestations into rigid schemata. This imperfection is exacerbated by changes with time, location, etc. Lowy therefore argues that nowhere outside medicine are there so many qualifications such as 'para' or 'pseudo' to any current taxonomy. In this, Lowy perhaps overstates her case for two reasons. All taxonomic systems are qualified, the provisos being a measure of the extent of knowledge of the time: thus ornithological taxonomy is full of subspecies, races, clines etc. – that is populations with similarities and dissimilarities which can only be accommodated within a larger classificatory umbrella. All scientific or medical catalogues (nosography) change more or less rapidly over time as modifying information, for example from genetic analysis, is adduced and collated. Further, terms such as pseudo usually have a specific meaning in medicine and often reflect the history of the elucidation of the condition: an example is pseudohyperparathyroidism which clinically appeared to share features with the nominate endocrine disorder but which is pathologically and biochemically distinct, even from a further variant, pseudopseudohyperparathyroidism. Despite these caveats, Lowy's argument that ontology is a compromise allowing ordering of observed phenomena is well made. To this must be added the usage of disease names as a convenient recognisable identifier of an agreed condition which allows discourse and interaction between doctors, patients and bureaucracies. Names may not necessarily represent current biomedical understanding but reflect an agreed compromise used to construct a working taxonomy accessible to all participants in the medical encounter. Generic terms such as cancer or fever lost their validity as medical knowledge and actors' understandings changed. Specificity instantiated by a unique name became the accepted language of medicine.

At any point in time the current definition of a disease 'entity' may be framed by some or all of: a patient-defined symptom complex, laboratory-defined parameters, or a professionally-defined deviation from the prevailing 'normal'. Each of these may be modified by political and economic factors or by public and professional perceptions (Cunningham 2002). Neither a disease concept nor its contingent variables are stable, each may change either independently of or dependent on the other (Wilson 2000). A disease is a definition in flux over time and with circumstance. There are no exemplar historical diseases, although specific categories have received historical study, each category of unwellness both conforming to and deviating from any chosen model of the framing of disease. Medicine is, and always has been, based on and constructed around disease, its study and treatment, its impact on individuals and society, and the social and individual physical and conceptual reactions to disease. Whilst the centrality of disease to medicine is indisputable, it is no more constant than its social or individual circumstance. In the same way that it is mathematically impossible to solve a multi-sided equation in which each factor may be constant or variable or both, it would appear not possible to gain a complete historical understanding of a disease, its circumstance and its time. Cunningham (2002, p34) suggests that 'disease' is so constrained by time and place as to make comparisons and histories invalid (what he terms 'incommensurability'). This argument holds only in so far as the meanings of names may become hidden, for which he chooses some extreme examples: thus the medieval 'sweating sickness' has no modern resonance. However, continuities in the generational meanings of, say, plague are sufficiently strong as to justify histories, bedded in time and place.

Nosology, the systematic classification or arrangement of disease entities, is often held to be the primary way of professional understanding and controlling the medical dialogue. Nosology (or nosography = systematic description of diseases) has been in the English medical parlance since the 17th century, but gained prominence following the work of Knud Faber[113]. In his most quoted book (Faber 1930), Faber uses nosography as a trope on which to build a history of medicine or, more precisely, a history of medical writers. He contended that describing and cataloguing diseases demonstrated the changing ways of thinking of physicians over time. By emphasising individual contributions (by Sydenham, Laennec, Bichat, Louis, Pasteur, Koch, Virchow, to name

[113] Knud Faber (1862 – 1956) was professor of internal medicine at Copenhagen and is perhaps best known for his studies of tetanus toxin.

but a few) he traced the history of medicine through clinical observation, anatomical description, and experimentation in physiology, bacteriology and genetics[114]. In so doing, Faber re-established the centrality of nosology in medical thinking, but does so by the story of the lead actors and not necessarily in the wider social context in which they worked. Inadvertently, Faber illustrates a cardinal feature of nosology: that it is time-constrained, limited by the knowledge of the period. Thus Faber recounted past ways of thinking such as English clinical observation, Parisian clinic-pathological correlations, and German laboratory studies. But he could not know of the revisionist understandings of disease provided by genetics, immunology or diagnostic technologies. He further demonstrated a limitation common to much historiography: that it is also geographically-constrained, concerned only with the Western way of thinking about disease.

Faber did, however, recognise that concepts and categorisation of disease were human abstractions, not objective entities. The measure of their truth was the pragmatic one of the degree to which they improve the precision of prognosis or therapy, or prediction and control. Disease names are therefore appropriate for practising rather than learned professions as they make rational clinical work possible. At about the same time, Crookshank (Crookshank 1930) was arguing that nosological entities ("Proper Names for Special Disorders") may act as a barrier, if mechanically applied, to the exploration of the individual patient's experience. He argued (as many have since) that the grouping of like cases as cases of the same disease is purely a matter of justification and convenience, liable at any time to supersession or adjustment.

Diseases with stable manifestations have varied in their social construct through time; one might cite epilepsy in this category. There are extremes ranging from almost exclusively social constructs, such as the Victorian concept of chlorosis (Figlio 1978; Loudon 1984) on the one hand, to apparently immutable disorders such as tetanus or bone fractures, the historical significance of which lies in the professional and societal reaction to them. In between are disorders such as plague or pleurisy which have over time changed their nature, the medical definition, and the social construct attributable to them (Cunningham 1992; Wilson 2000). Confusingly, the nature of disorders with a 'modern' closed definition may change with time. Instantiating examples include the changing pattern of streptococcal infection in the middle of the twentieth century: the virtual disappearance of scarlet and rheumatic fevers and of epidemic post-streptococcal

[114] This sequence is repeated in the description of individual disease entities: a case of ontogeny repeating phylogeny?

nephritis, which not was overtly related to changes in medical practice; thus the definitions remained constant, the inconstancy being inherent in the disease.

Rheumatic fever[115] provides an elegant comparison with which the framing of ARF can be paralleled. Both conditions appeared to arise anew and have complex and contested definitions resulting from what Lowy has called 'mediating thought styles' bridging between heterogeneous elements in complicated systems (Lowy 2011). This linkage between material entities and actors' practices favours the rise of new entities. As Amsterdamska argued, the attitude towards and taxonomy of changing diseases results from an interaction between two sets of cognitive restraints imposed by the biological knowledge of the time and by the changing concerns of clinical practice (Amsterdamska 1987). Rheumatic fever, as English records, was elusive and complex and did not exist in the medical mind before the 19th century (English 1989; English 1992). Its 'discovery' occurred at a time when medical institutions, technology and ideas were also evolving: a situation comparable to that surrounding ARF a century later. The disease, the actors, and the conceptual frameworks were all changing over time – a dilemma as applicable to ARF as to rheumatic heart disease. Both disease concepts were constructed in a typical sequence: narrative case-histories to which were added a "revelatory coda" in the form of post-mortem results; later the disorders were represented as numerical aggregates summarising hospital experience. Eventually both were depicted as a linked cluster of symptom configurations legitimated by supporting diagnostic technology. What English says of rheumatic fever is equally relevant to ARF: that the naming of the disorder provides "a viable – if schematic – compromise between a unified yet abstract clinical entity and its protean manifestations…" Yet Kunitz cautions that the application of a diagnostic label could become an example of modern word magic, mistaking the word for the thing to which it refers.

Scholars have at times attempted to impose order on the insoluble by assuming constants, the most obvious example being that the disease is naturally constant over time, the sociological reaction(s) being the variable(s). An illustration may be provided by cholera, the subject of much work in the history of public health, social determinants of its epidemiology, social and medical responses to epidemics. This work, at least covertly, assumes that the currently accepted medical definition of cholera (an acute

[115] Rheumatic fever is a complex disorder which in the past not infrequently followed streptococcal throat infections. Manifestations include carditis (leading to chronic damage to the cardiac valves), polyarthritis, chorea, and a distinctive skin rash. It became rare in the late 20th century, either because of widespread use of antibiotics or because of changes in the causative organism.

illness of profuse rice-water diarrhoea associated with the faecal-oral transmission of the *Vibrio cholerae*) is in fact identical to the disease called cholera in the past[116]; yet in the middle of the 19th century the medical name of this disease was qualified by adjectives such as English, Asiatic, morbus (assuming that the naming of the object is short-hand for its definition) and, on the other hand, the appearance of the el Tor variant of the causative organism in the late 20th century changed not only the epidemiology but also the social response to the disease. Retrospective application of present definitions may obscure both the medical and social significance of a disease: the social impact of syphilis in the Renaissance and in the 19th century was dramatically different, but then so was the disorder itself, its manifestations being shaped by its 'medical' characteristics which in turn shaped the personal and public responses, which then redefined the disease until laboratory and therapeutic considerations demanded further re-evaluation of the medical concept, an iterative process that is conceivably indefinite and infinite.

3.2 The case for disease identification

The framing of the disease, disorder or syndrome called ARF may be put into a broader context. There are questions about what preceded and succeeded the apparent discovery and definition of ARF in the 1940s. These questions have been summarised by Rosenberg ((Rosenberg 1992), p20), considering the definitional ambiguity to which I referred:

> "Each generation of physicians can call upon a different repertoire of framing materials in suggesting an understanding of pathological phenomena; but the phenomena may also change…[creating the]…complex or elusive aspect of disease history…This timing poses an intricate and intractable, yet highly significant, dilemma. How does one make sense of this interactive negotiation over time, this framing of pathophysiological reality in which the tools of the framer and the picture to be framed *both* may well have been changing…"

Disease is the essence of medicine; the history of medicine is the history of the personal, professional or institutional interaction with disease, however that may be understood at the time. A large sociological literature is devoted to the construction of disease, illness, or deviation from the prevailing concept of wellness. The circumstances defining disease and the repercussions of such definitions have attracted much scholarly historical attention. Medical literature, whilst frequently acknowledging what is

[116] "There is a tendency in ontology to consider disease entities as persistent and to corroborate the specific nature of a disease by tracing its existence through the ages." Temkin 1977 p449

perceived to be the 'landmark' description or 'discovery' of a disease, rarely reflects on the changing understandings of a condition and how these have influenced past, and continue to influence present, practices and attitudes. At any point in time, the medical perception was and is that a disease category is stable. Knowledge may be added, treatment may be modified, prognosis or epidemiology may change, but the fundamental definition of a particular disorder appears immutable over time and place. This is a fundamental misreading of the nature of 'naming' of disease, a process which attempts to convey the current understanding of a complex situation in a convenient manageable term. The key to this is not only 'current' but also the name of the moment is a 'convenient' title that seeks to encapsulate specific unique features of the disease at that time: whether it be an eponym or a description, it is imagined to be a universally acceptable unambiguous identifier.

Lawrence, in the prologue to his consideration of the framing of coronary thrombosis as a disease entity, places the 'problem' of the belated recognition of the disease[117] in historical context (Lawrence 1992), and his comments are equally applicable to the recognition of ARF as a separable medical condition :

> "… the focus of enquiry should be on how communities come to see or frame diseases, indeed in some cases…to see them so clearly that nonmedical individuals can recognize them. What is required is an explanation of how and why perceptions are structured and how and why they change…not a negative process of removing obstacles but a positive restructuring of clinical and pathological experience. Further, the features held to be characteristic of the disease were not suddenly recognized but were arrived at by a process of negotiation and persuasion over a period of time." (Laurence 1992, pp 52-54)

By utilising a sociological modification of network theory (Hesse 1974; Bloor 1982), Lawrence (1992, pp54-55) presents further observation and opinion that are perhaps even more applicable to ARF:

> "I suggest that in the reclassification process that gave rise to the disease the cognitive and social interests of…physicians determined the emergence and form of the new disorder. These interests led to the creation of a syndrome that offered great potential for epidemiological work, had therapeutic possibilities, and could be the focus of pathological, physiological, and technological research…in defining a…"definite

[117] "In retrospect, this generation of physicians were puzzled at their earlier failure to recognize so apparently distinct condition. (Lawrence 1992, pp 51/52).

and material" disease these clinicians were also defining their own social identity. The demarcation…was a means of signalling their own medically elite status. Conceptual redefinition was part of the process of specialty formation."

Lawrence is at pains to demonstrate how the British academic cardiologists of the 1920s and 1930s, in framing and promoting the diagnosis of coronary thrombosis, endeavoured to establish its medical lineage back even as far as William Harvey[118]. By establishing a provenance for the disease, they made it a 'respectable' condition embedded within the medical tradition.

Conversely, the newly-established nephrologists of the 1940s took pride in collecting and collating this 'new' condition and rarely if ever referred to any pre-1940 clinical papers. Thus, in their epochal paper, Swann and Merrill observed: "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" (Swann and Merrill 1953). These American academic nephrologists were making a bold statement: in effect that a new important syndrome had been discovered; the concept had been rapidly and completely elucidated by the application of the best modern scientific laboratory medicine; and, further and most significantly, they had a new technology which, if judiciously applied in expert hands, would maintain the patient through the critical phase of the illness, allowing recovery from an otherwise fatal condition. This was a statement of confidence: a new breed of physicians had named a disorder emblematic of modern medicine, under difficult circumstances, and in doing so had completed the circle (diagnosis-conceptual understanding-effective treatment) by employing all the benefits of the new technological medicine. It was certainly a powerful statement establishing their self-adduced specialty. They had no need to seek precedence from the 'ancients', this was a thoroughly modern affair.

This contrasts with Lawrence's view that the "new syndrome" arose from "a slow negotiation of the features of the disease as part of a reclassification process" (Lawrence 1992, p62) and "Framing the new disease involved an assertion that it had, and always had had, an existence." Whilst Lawrence argues the importance of establishing antecedents as positive assertions not only to bring the disease into existence but also to establish its character and qualities, the nephrologists of the 1940s, who were struggling

[118] ibid p63: "Thus its existence was grounded in its having a past". p64: "By creating a history for this disease it was possible to diagnose it retrospectively in the works of the great clinicians."

to establish themselves as a distinct specialist elite, took no cognisance of events before the 'big bang' of 1940. It is noteworthy in this context, that none of the innovators of clinical dialysis made any reference whatsoever in their publications to any of the pre-war work in this field. It was as if all were setting their specialty 'clock' to a new time scale firmly situated in the present. By formulating ARF as a new disorder (and one, moreover, that they controlled) they stated that their modern scientific and technologically-daring medicine was completely distinct from, and superior to, the preceding empirical and conservative medicine. They were the new leaders of the new medicine, entirely in tune with the confident optimistic ethos of post-war American medicine (Starr 1982; Stevens 1989; Berg 1995) which saw itself, by its espousal of pure and applied clinical science, as a stepwise progression in the practice of medicine. Undoubtedly, Lawrence's social constructionist analysis of the framing of coronary thrombosis as a disease and its relevance to the separation of the specialty of cardiology ("Lines were drawn around a discipline and the disease it studied. A definite (natural) entity reproduced the material arrangement of men" p75) is directly relevant to the framing of ARF and nephrology. The mechanism was slightly different.

Acknowledging that modern medical practice is predicated on diagnosis[119], Rosenberg further develops this approach to disease-framing (Rosenberg 1992, pxii) by saying that "…disease is at once a biological event, a generation-specific repertoire of verbal constructs reflecting medicine's intellectual and institutional history, an occasion of and potential legitimation of public policy, an aspect of social role and individual…identity, a sanction for cultural values, and a structuring element in doctor and patient interactions.." He further acknowledges the circumstances of disease-framing[120] and elsewhere he neatly and succinctly identifies the conceptual paradigm shift which allowed ARF to be delineated:

> "…the interests of a physiologically oriented and self-consciously scientific generation of nephrologists turned to functional criteria, supplanting the

[119] Rosenberg 1992, pxii fn 2: "Disease can and must be seen as a taxonomy – with individual ailments arranged in some order-imparting structure." Rosenberg 1992, pxiv: "Disease concepts imply, constrain, and legitimate individual behaviours and public policy."

[120] "Physicians have always been dependent on time-bound intellectual tools in seeking to find, demonstrate, and legitimate patterns in the bewildering universe of clinical phenomena they encounter in their everyday clinical practice: (Rosenberg 1992, pxvii)
"In crafting an explanatory framework physicians employ a sort of modular construction, using intellectual building elements available to their particular place and generation. But the resulting conceptions of disease and its hypothetical origin are not simply abstract knowledge…" (Rosenberg 1992, pxviii)

anatomical, lesion-oriented conception of disease so influential in previous decades…"[121]

In an essay on what he terms the 'tyranny' (or 'indispensability') of diagnosis, Rosenberg makes further points of direct relevance to the conceptualisation of ARF, and the consequences of this (Rosenberg 2002). Within "the contingent and situated quality of medical knowledge":

"…disease could now be operationally understood and described. It was measured in units [blood urea and creatinine for renal failure], represented in the visible form of curves or continuous tracings [≡ laboratory printouts], and taught to successive generations of medical students." "Now disease was equated with specificity and specificity with mechanism, while all the while decoupling this increasingly ontological conception from idiosyncrasies of place and person." (p242)

Thus, for ARF, the physiological studies of water-electrolyte balance[122] (the 'esoteric knowledge base' (Peitzman 1988; Peitzman 1992)) together with developments in clinical analysis such as the flame photometer (Peitzman 1988; Cameron 2002; Peitzman 2010) allowed the definition of ARF by biochemical laboratory criteria. ARF may have been the stimulus for the adoption of renal biopsy to differentiate acute potentially reversible renal impairment from chronic renal failure, at that time untreatable (Iversen and Brun 1951; Wilson, Turner et al. 1976; Peitzman 1988), but the primary use of percutaneous needle biopsy of the kidney is, and has been, for the pathological diagnosis of intrinsic renal disease (glomerulonephritis) which only occasionally presents as ARF (Cameron and Hicks 1997).

Rosenberg (2002, p245): "That intellectual centrality [agreed-upon diagnostic categories] was, to a degree, embodied in the beginnings of specialism…" In no situation was this truer than for nephrology. Prior to the 'discovery' of the syndrome that came to be termed ARF, there was little or no clinical need for specialist renal physicians – kidney failure, when recognised, was managed by diet, regimen, rest and

[121] Rosenberg, untitled preamble to Peitzman, S. J. (1992). From Bright's disease to end-stage renal disease. Framing Disease: Studies in Cultural History. C. E. Rosenberg and J. Golden. New Brunswick, Rutgers University Press**:** 3-19. p4.

[122] Peitzman 1988, p233: "Assembled before World War II by metabolic-physiology workers…, an ordered knowledge of extracellular fluid balance was crucial for the development of clinical dialysis." However, as previously mentioned, the early inventors of clinical dialysis made little if any formal acknowledgement of previous work. It is as though they assumed an understanding and adopted a technical 'fix' that fitted this acquired and assumed knowledge. It was only later that the 'scientific' rationale for the procedure was retrospectively applied.

encouragement, all comfortably within the compass of a general physician[123]. Thereafter, ARF provided a *raison d'être* for the renal specialist[124]. Again, Rosenberg summarises the generality which can be directly applied to nephrology (Rosenberg 1988, p51):

> "The boundaries of the new concept…mirror a fundamental social reality: the creation of a…somatic and technical cognitive identity that would clearly define and legitimate the specialty, setting it categorically apart from that of other clinicians."

As noted, perhaps with a touch of world-weariness, by a distinguished academic physician: "…specialties thrive in situations where something can be offered, but where that something is complex, and only partially effective" (Beeson 1980). Nowhere has this been more apparent than in the iterative and self-fulfilling relationship between ARF, nephrology, and dialysis. "This linkage among procedures, machines, and diagnosis seemed to the majority of physicians both desirable and inevitable, for disease could now be defined in increasingly objective terms." (Rosenberg 2002, p247)[125]. Thus Cameron argues:

> "…one can make a good case that the *availability of new treatments*…in the 1940s focussed attention on this diverse group of patients, who were now identified as for such intervention, and led to the global concept of 'acute renal failure'." (Cameron 2002, p113)

This case[126] has been argued more forcibly by Peitzman, showing the linkage between the diagnosis and the treatment, each reinforcing the other, but each dependent on the

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[123] Peitzman 1988, p223: "But even for the internist with special interest in disease of the kidney, there existed no basis for in-hospital renal consultation until…the rediscovery and definition of acute renal failure... Acute renal failure called for the display of special expertise in the ward and would provide impetus for special techniques – renal biopsy and dialysis." "From about 1946 through 1955 acute renal failure increasingly captured the attention of internists interested in renal disease…diagnosis and treatment…required consultative expertise in the hospital, and the expert might make a difference. Careful attention to the management of electrolyte and acid-base disorders might help the patient survive into the 'diuretic phase'…thus the appearance of acute renal failure as a new entity exercised the practical arm of the renal specialist as nothing else had before."

[124] Peitzman 1988, p227: "The primary reason for calling the nephrologists remained acute renal failure. More and more patients survived shock, surgery, trauma and other calamities, but caught acute tubular necrosis along the way. New nephrotoxic agents displaced mercury and sulfa drugs as tormentors of kidneys…"

[125] In another context, Rosenberg said (1992, p20): "…all these efforts sought to generalize a valid clinical entity from among the disparate symptoms of an extraordinary variety of cases, no one of which might stand as ideally typical with entire precision…appealed to contemporary practitioners."
"…the interdependence of treatment and of the idea of disease is a very real one…Treatment can determine how disease should be considered." Temkin 1977 pp453-4

[126] "Disease entities became more plausible, more sharply defined, and more frequently the framework and rationale for predetermined therapeutic interventions. Once articulated, these entities have helped order the relationships among machines, experts, caregivers, and patients in the hospital, creating a structure of seemingly objective priorities and practices." (Rosenberg 2002, p249).

intervention of the specialist nephrologist (Peitzman 2001)[127], who acts as "a kind of interface manager shaping the intersection between the individual patient and a collectively and cumulatively agreed-upon picture of a particular disease and its optimal treatment."[128]

Defining the diagnosis of ARF and proffering a potentially palliative treatment released consequences which not only sharpened the identity and authority of nephrologists but also radically changed medical practice and health care delivery. This has been addressed by Rosenberg (2002, p248):

> "…therapeutic innovation and a growing diagnostic capacity have defined and legitimated disease concepts as they have empowered medical practitioners and reconfigured lay expectations of medicine. Such innovations have even altered the ecology and manifestations of…new diseases, given shape, texture, and often a greater degree of predictability through the agency of medicine even when they could not be definitely cured…the predictability of a response to a particular agent implies the specificity of the pathological mechanism and hence its epistemological legitimacy. This circular – and self-fulfilling – tightness of fit has historically provided evidence for the hard, sharply-bounded, and mechanism-legitimated definition of disease entities. Because most somatic disease categories seem in themselves value neutral…and thus legitimate care, there seems something wrong in not treating the sick when an efficacious technology is available and mandated by a particular diagnosis."

This 'technological imperative' must have been a powerful motivation for the dissemination of dialysis, and the creation of renal physicians, to treat ARF.[129]

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[127] "The idea of dialysis in the care of patients with acute renal failure appealed powerfully to therapeutic logic: acutely injured kidneys will often get better after a nearly predictable period of obstinate nonfunction; patients may feel wretchedly ill and even die during the anuric phase; the artificial kidney used once or even a few times can lessen the sickness and prevent the patient's death; then, once renal regeneration prevailed, it need visit the patient no more. The dialysis machine thus appears as a specific treatment prescribed for a limited time, facilitating if not precisely creating a cure – a restoration to a prior state of unimpaired health and bodily integrity. This is the most pristine and desirable medical story: diagnosis, efficacious treatment, cure. Of course, the actual events of acute renal failure did not and still do not always work out so cheerfully: neither native nor artificial kidneys necessarily follow the textbook drill. But the principle remains impeccable." (Peitzman 2001, p201)

[128] Rosenberg 2002, p253

[129] "During the 1950s, clinicians saw that the artificial kidney could reverse the symptoms and chemical excesses of patients with acute renal failure, and they occasionally showed that it could keep an oliguric patient alive beyond the point where most such patients would die…How can it not be offered to patients suffering the ailments it corrects?" (Peitzman 2001, p200)

How the syndrome of ARF was clinically constructed will be reviewed later, but further examples of the wider implications of the relationship ARF ↔ renal physician ↔ dialysis require mention. As with all medical innovations, dialysis was initially used only in the most desperate cases, patients *in extremis* in whom all other (conventional conservative) measures had failed. Consequently, it could be argued that failure of treatment was not due to inadequacy of the technology but rather to the fact that the patient's condition had progressed beyond the point of reasonable expectation of recovery. The patient had been referred too late and/or the treatment unreasonably delayed. It therefore followed, according to the protagonists of dialysis, that earlier application of the technology, and in higher 'doses', would be more successful.. This might be a self-fulfilling prophecy in that patients were now considered for treatment earlier in the course of their disease, a decision based not on the patient's symptoms but on sequential laboratory data and the renal specialist's prognostication. This would inevitably include some individuals who might spontaneously recover. In any event, the survival of treated ARF seemed to improve. But the condition known as acute renal failure itself changed with time[130], becoming more complex and incorporating a wider range of patients and of precipitating conditions (Turney, Marshall et al. 1990). Later observers, noting that the overall mortality from ARF had not improved after the 1960s, argued whether the provision of more dialysis was *per se* beneficial, or conversely whether dialysis itself hindered the renal recovery from ARF (Stott, Cameron et al. 1972; Conger 1990; Turney 1990; Turney 1992; Turney 1994; Turney 1996). This change of practice had some unintended consequences: firstly, it increased the demand for dialysis for ARF (and hence the demand for nephrologists) and, secondly, it required modification of the dialysis technology to allow more frequent and more prolonged usage, a key factor in the subsequent adaptation of the technique to maintain patients with end-stage renal failure (Scribner 1990).

Later still it was demonstrated that *any* perturbation in kidney function in a hospitalised patients adversely affected the outcome of their primary disorder (Levy, Viscoli et al. 1996). This redefinition of acute renal dysfunction was based on the

[130] "More and more during the 1970s and since, renal failure was seen not as an isolated finding but in a setting of multiorgan failure (a term probably first used in 1973) and sepsis, particularly the 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…,the mortality of 'acute renal failure' has, if anything, increased slightly during the past five decades. But today it is a different condition." (Cameron 2002, p222).

statistical analysis of biochemical data, i.e. was completely removed from traditional bedside clinical assessment. ARF had become more firmly a disease of the serum creatinine. The centrality of the laboratory-based mathematical formulation of the configured definition of kidney failure is lucidly described by Peitzman (1989, p26):

> "An elevated creatinine in a patient *is* 'renal failure'…It does *not* call to mind an anatomic image…For the nephrologists…, the serum creatinine does, however, have associations, is more than an abstract number…a creatinine of 'ten'…conveys far more than twice the urgency of a creatinine of 'five'…As with the tone of a clarinet, qualitative changes occur as one goes up the scale of serum creatinines"

It is now perfectly feasible for the physician to diagnose and manage renal failure at a remove from the patient – diagnosis and treatment prescription based on laboratory numbers, dialysis delivered by a nurse or technician, sophisticated dialysis machines monitoring and controlling themselves. A far cry from the intimately 'hands on' approach of the early nephrologists. The evolving concept of ARF not only provided the motor for the creation of the specialty of nephrology and its technology, but continued to maintain and reinforce them.

3.3 Building on cases

Disease recognition and delineation is generally assumed to follow a progression from a symptom complex, recognisable as distinct by clinicians or even laymen, through the association of symptoms with distinct gross, and later microscopic, morbid anatomy, to laboratory confirmation by bacteriology, biochemistry, etc. The laboratory way of thinking subsequently provides causal explanations (pathogenesis) and, perhaps, treatment (therapeutics). The process is one of iteration, redefinition and refinement. Whilst this historical approach can be sustained for potentially identifiable conditions viewed in long retrospective from present-day disease definitions (Wilson 2000), the assumption accepts that a disease is present in recognisable, albeit incomplete, form in the medical knowledge-base before it is reconfigured into its final, complete form by the anatomical and laboratory traditions. Whilst this argument may be acceptable for relatively straightforward conditions with a long history, it becomes more difficult to sustain for disorders more recently separated from the mass of human ills. As an example of the former, tetanus was clearly recognised in all cultures at all times (all the salient clinical features of contaminated wounds preceding muscular spasms and death are described in the Hippocratic corpus) by lay and professional alike. The eventual identification, centuries later, of the causative organism and its spores provided the

ostensibly incontrovertible laboratory imprimatur on the disease definition. This new knowledge allowed the development of therapy (antitoxin, immunisation). The circle of symptoms-cause-mechanism was completed by application of knowledge of neurotransmitters, confirmed by laboratory experimentation.

This linear and sequential process is only in part applicable to 'new' diseases because the chronological approach reflects a tendency rather than a clear-cut periodisation and several categories may coexist in time, with the narrative of continuity potentially obscuring important changes.. Consideration of such chronologies has focused on the confirmation of disease by laboratory techniques or applied technology and the dissemination through the profession of 'new' concepts (Lawrence 1985; Lawrence 1992; Peitzman 1992). To the scholarly reviews should be added consideration of the mechanism by which a disease may become defined within the medical mind; that is to say, become recognised as a discrete clinical problem with some identifying features that give it distinction from other problems.

There is no convincing instance in which the 'laboratory tradition' (Cunningham 1992; Cunningham and Williams 1992; Jardine 1992) has defined a disease *ab origine.* Before the laboratory comes the unwell patient, in the absence of whom the laboratory would not be interested or involved. The unwell patient is a clinical problem, a 'case', which requires an observer to recognise or hypothesise some distinctive aspect and to record and disseminate these clinical features. The accumulation of cases, the collection and collation of their identifying features, is what defines disease clinically, practically, and recognisably. A single case-report does not constitute a disease, merely a medical curiosity. The collection of repeated clinical observations (a 'case-series') is the seed of a disease definition. The analysis and synthesis of repeated cases, defining their characters and their commonalities, becomes accepted as a 'disease' recognisable by others, a diagnosis, a stimulus for further clinical observation and recording, and for the application of laboratory techniques to add 'scientific' credibility and definition. The analogy must be English common law, based on the accumulation of carefully recorded, annotated and analysed individual cases, in which the facts and opinions or decisions in each are documented and weighed. The individual case becomes significant solely through the principle of precedence – subsequent cases are decided against the facts and outcomes of those going before. Comparisons and decisions may only be made if there is an available body of published records: Law Reports or medical case reports. To be acceptable, the documentation must be factual, complete, and refer to precedence. When

constructing the composite description that is the 'type', weight is given to characters that appear common to all cases, within the perceived confines of the condition. Inconstant features, even if illuminating, are given less weight and are rejected as atypical. This may result in so narrow a definition that each case may be perceived as individual, not aggregated into a disease. A dramatic feature may be elevated to cardinal importance, distorting the generality[131] whereas less obvious features may be essential, fitting best with the ultimately chosen definition. This is dependent upon the retrospective analysis of accumulated experience, presupposing adequate numbers of typical specimens.

A number of scholarly works have visited the ways by which scientific thought and understanding have been constructed (see, for example, works by Hacking, Kuhn, and Pickstone). This historical and philosophical analysis has been directly applied to medicine and, within it, not only to the process of disease identification and naming but also to the variously contested interaction between science and praxis (see, for example, Lowy, Pickstone, Sturdy, and Warner). Particularly apposite to the disease-framing process are those works built on the theories of Thomas Kuhn (Kuhn 1977; Kuhn 1996). Kuhn convincingly argued that scientific knowledge production proceeds on a case-by-case basis, using previously solved 'puzzles' as 'exemplars' (or 'paradigms') for the solution of new problems. Sturdy has shown (Sturdy 2007) that medical cases (specifically exemplary cases of diseases) are perfectly compatible with Kuhn's concept of scientific knowledge production as "puzzle-solving". Indeed one might argue that constructing disease entities from accumulated paradigmatic medical cases is the pristine exemplar of Kuhnian reasoning.

The trope of building by cases has influenced much recent writing on medical thinking. So, for example, Forrester argued that the role of cases in the construction, in addition to the practical application, of scientific knowledge has been under-appreciated – most specifically in relation to medical knowledge (Forrester 1996). Consequently, he adds a seventh style, that of reasoning in cases, to Hacking's highly influential work on the 'styles of reasoning' in scientific discourse (Hacking 1990). All of Hacking's 'styles' are to a greater or lesser extent applicable to medical reasoning and understanding: the

[131] In the present context, the crush syndrome as originally described did distort the potential understanding of the generality of ARF. The immediacy of the focus on traumatic muscle injury threatened to divert the medical gaze away from the ubiquity of the renal response.

styles are not discipline-specific but encompass the range of scientific philosophy[132]. Despite the utility of Hacking's thesis, it does not accommodate the observed and recorded behaviour of doctors who, as Sturdy shows (Sturdy 2007; Sturdy 2011), think and understand in cases, in both their research and their patient-encounters.

The Kuhnian case-by-case reasoning is nuanced, indeed situated, by the medical way of thinking, as eloquently enunciated by Stephen Toulmin (Toulmin 1976). Toulmin considers the ways in which doctors think in different situations, the modes being comparable to Hacking's styles. These ways combine to form hybrids in particular circumstances, but the focus of attention remains the case. The medical way of thinking is usefully interpreted by Susan Leigh Star's concept of triangulation: the combination of clinical and laboratory observation to produce an understanding that simultaneously explains the case in hand and contributes to more general theories (Star 1989).Sturdy has summarised the work of Toulmin and of Kathryn Montgomery (Montgomery Hunter 1991; Montgomery 2006) by describing medical knowledge as narrative, hermeneutic and holistic. With the possible exception of elements of public health, the medical encounter is case-constrained and medical knowledge, education and practice are predicated on cases, either individually or in groups or series.

Hess and Mendelsohn have argued that seriality is the basic operation of medical understanding, collected patient histories (cases) being the stable centre of medical knowing. They further contend that the organisation of series is based on and through paper records and publications (Hess and Mendelsohn 2010). Record keeping, the internal structure of which became formalised from about the 1890s, is the anamnesis of the medical profession. The systemisation of records, in which a rigidly structured account moves from first impressions to hypotheses to firm diagnosis, is dependent on medical assumptions, priorities and beliefs so that the data produced by technologically sophisticated diagnostic tools outweighs the patient's narrative in diagnostic importance and credibility (Epstein 1992). The negotiated assumption that a raised serum creatinine is the absolute criterion for the diagnosis of ARF would seem to bear out this proposal.

The syndrome of ARF, as formulated in the 1940s, was defined by clinical circumstance, timescale, urine output, blood chemistry, and recoverability (with or without dialysis). Accumulating experience showed that circumstances were legion,

[132] Hacking delineates six styles of reasoning: postulation and deduction, experimental exploration, hypothetical construction of models by analogy, ordering of variety by comparison and taxonomy, statistical analysis of regularities of populations, historical derivation of genetic development.

urine output unreliable, there was some variability in time, and recovery was not inevitable even with dialytic support. By exclusion, and because of continuing doubts about the exact pathological processes involved, blood chemistry became the defining principle. When the definition of acute renal dysfunction had become, essentially by default, a short-term deviation from the accepted 'normal' the debate shifted to what degree of deviation was clinically relevant, determining both 'illness' and outcome, and what deviation justified intervention. Initially dialysis-recoverability became both the definition of the disease and the goal of its treatment.

The motivation for reporting clinical cases has multiple drivers. Recognition of the unusual or of instructive instances requires clinical knowledge derived from teaching and experience. This is clinical acumen which is prized and acknowledged by fellow practitioners. The reporter must demonstrate erudition, which is academic knowledge of the subject and its precedents. There must be authority that the case is complete, the appropriate investigations performed adequately, and alternatives excluded. Acumen, erudition and authority are sought after professional attributes and in themselves are motivations enough in a competitive arena – competing for status. Publication is the benchmark of professional achievement: kudos is derived from publication especially in the 'big names' in the hierarchy of medical journals; there is a desire to add to the community of knowledge, however small the addition; publicity for both the case and the author; recognition and publication of 'interesting' cases is seen as a measure of an enquiring and educated professional mind. This mind is, of course, framed by the education received by students and junior doctors in their formative years. Conventionally dated to the 'Parisian school' of medicine (Maulitz 1990), the training of medical students remains strongly case-orientated (Lawrence 1993): individual patients encountered when 'walking the wards', illustrative cases used to focus formal teaching, the pervasive ethos (carried forward into their daily practice by the majority) of the singular importance of the patient in front of the practitioner at a specific time. As Montgomery has documented (Montgomery Hunter 1991; Montgomery 2006), the narrative basis of the entire medical encounter is all-pervasive. The significance of cases as the basis not only of the conventional practice of medicine in its widest sense, but also of disease definition is perhaps self-evident and has been reinforced by the occasional example of the 'first' patient, the type case, receiving eponymous immortality in disease names (for example, Christmas disease).

Although personalised cases are embedded in the fabric of medicine, individual cases are potentially shaky foundations for disease definition. Often portrayed by detractors as simply anecdotal and by definition subjective, because they are not subject to the rigours of scientific method, they are impenetrable to statistical analysis, and are often published in the least rigorously edited parts of journals, such as correspondence columns. Whilst these criticisms have undoubted merit, they are directed at an altogether different way of thinking. Case reports are 'natural history' as opposed to 'experimentalism' (Pickstone 2000). Each individual specimen has little hermeneutic value but, like a building brick, gains value when joined with other cases or series, then analysed and reviewed to find the significant commonality between each individual. It is collection and analysis that provides the bridge between the two apparently disparate ways of thinking. Analysis proposes the defining points of the disease; collection of cases provides the precedence or reference point for each subsequent case. The analysed dissected features gain acceptance when communal experience realises their functionality as the 'definition' of the disease, each subsequent case being tested, albeit often informally, against the reference. This community-wide knowledge is achieved by publication, oral or written, of cases to share the knowledge between professionals. If the knowledge is felt by this group to be sound and constant, and even perhaps subjected to some form of experimental or statistical probing, then the condition is agreed to be a 'disease' and added to the medical lexicon. Only then is the disease amenable to laboratory study or therapeutic intervention. The collection of curiosities is a time-honoured tradition, no less (but differently) scientifically valid (in the sense of knowledge) than experimentation or technoscience.

The concept of ARF grew from a plethora of seemingly disparate case reports, most lying in obscurity because of their apparent lack of concordance with others, but some having an immediate impact, stimulating the search for comparable cases and the wider enquiry into the laboratory correlates of the clinical problem. Initial thinking was focused on the causes of the acute kidney injury, leading to specialists thinking that the clinical problem was particular to their own field of expertise, be it obstetrics, trauma, poisoning. Collection, review and analysis of isolated cases demonstrated, by common consent, the centrality of a specific kidney injury and its functional outcome (Maegraith, Havard et al. 1945; Lucke 1946; Oliver, MacDowell et al. 1951; Oliver 1953; Swann and Merrill 1953). Attention was diverted from the antecedent causes to focus on a unifying concept of ARF; for example, from obstetric disasters to the realisation (Young and

McMichael 1941) that these damaged kidneys were indistinguishable pathologically and functionally from those of patients with traumatic rhabdomyolysis, malaria or mercury poisoning (Foy, Altmann et al. 1943; Maegraith, Havard et al. 1945). The consequence was a disease definition accepted in practice and from which flowed laboratory enquiry, therapeutic interventions, and indeed the specialty now called nephrology (Peitzman 1992). Arguably, this all started with four cases injured in the Blitz (Bywaters and Beall 1941).

3.4 Publications and journals

There is a convention that scientific publications are prefaced by an introduction summarising what is known on the subject of the paper (Bynum, Lock et al. 1992). Whilst these introductions may be partial or selective, they are essentially an 'historical' record of accumulated knowledge, as well as being an acknowledgement of previous work[133]. Readers are expected to assume that the introduction is full and balanced, which may not necessarily always be the case. Bywaters and Beall in their epochal paper incorrectly offered the crush syndrome as an entirely new clinical entity (Bywaters and Beall 1941; Bywaters 1990). This may have been a small factor in achieving the prominence of the paper, although the impact derived mostly from the description of a dramatic medical complication of events upon which the entire population's thoughts were focused, the Blitz[134]. In follow-up publications (Bywaters, Delory et al. 1941; Bywaters 1942; Bywaters and Dible 1942; Bywaters, Crooke et al. 1943; Bywaters 1944; Bywaters 1945; Bywaters and McMichael 1953; Bywaters 1990; Bywaters and

[133] "Above all…listing debts, debts of information or of inspiration." Richardson, R. (2008). The Making of Mr. Gray's Anatomy. Oxford, Oxford University Press. p154

[134] The immediate response to Bywaters and Beall in the correspondence columns of the *British Medical Journal* is of interest. HA Harris, Professor of Anatomy at Cambridge (BMJ 1941; 1:491) castigates them for their intrusive investigations and advocates a wholly Galenic approach to these cases: "Crush injuries are not new. They are commonly seen on the coalfields, where the treatment is careful nursing and non-interference rather than physiological and biochemical assay…The cases from the Postgraduate School suggest a syndrome which might be dubbed "continuous interference syndrome"…The main objection… is to the volumes of fluid injected…We require not only charts of blood chemistry and urine analysis, but something which will be as effective to the injured as colostrum is to the new born mammal. "Poor Tom's a-cold."" Thus the voice of conservatism was not only raised later against the mechanical treatment of ARF but also to the equally conflicting culture of clinical investigation at the Hammersmith

In contrast, a letter (BMJ 1941; 1: 491-492) from the "Surgeons, sector VI, E.M.S." [i.e. the Hammersmith] provides a modulated correction of Bywaters' paper, which has previously been overlooked. In particular, RH Franklin and DM Douglas provide a very clear description of the clinical scenario, the importance of which they had in fact reported six months previously (BMJ 28 September 1940, p432): "These three phases – a comparatively good condition on admission, a delayed peripheral circulatory collapse which responds to transfusion, and finally progressive renal failure…" They also emphasised a point of clinical significance which had been suppressed by Bywaters' chosen nomenclature, an observation later rather overlooked because of the dramatic overtones of "crush": that the key to the tissue damage was the duration of compression.

Beall 1998) earlier, predominantly German, clinical descriptions of the condition were acknowledged. In fact, the acknowledgement of the not insignificant preceding literature was incomplete, raising the possibility that wartime induced a reluctance to admit to German priority. There was also the problem of language: German papers of the 19th and early 20th centuries were written in 'high Deutsch', and therefore largely inaccessible to the majority of English-speaking medical readership. (This problem was resolved by the post-war Anglophone hegemony, which constrained the use of all other languages in mainstream medical publishing.)

A search of pre-1940 German literature reveals that the crush syndrome was clearly described (Colmers 1909) following the Messina earthquake the aftermath of which was so evocatively described by Axel Munthe (Munthe 1929)[135], and particularly in battle casualties in World War 1. The German military described in detail, both clinically and pathologically, crush syndrome resulting from burial in trenches collapsed by shellfire (which they named 'Verschuttung') (Frankenthal 1916; Borst 1917; Hackradt 1917; Frankenthal 1918; Kuttner 1918) and the experience was collated in the official German report on WWI military medicine (Kayser 1922). Significantly, these reports of ARF from pressure necrosis of muscles from verschuttung differentiated the condition from the relatively frequent (but still uncharacterised in modern literature)'trench nephritis'(Atenstaedt 2006). It is of some interest that an Allied report on war nephritis confused the two conditions, but contains good descriptions of traumatic ARF (Davies and Weldon 1917). The German reports, which were summarised in an accessible review (Minami 1923), clearly identified the striking contrast between the pronounced renal tubular changes and the minimal glomerular lesions. That is to say, they characterised the cardinal feature of the histology of the kidneys in ARF (acute tubular necrosis). In contrast to the detailed and accurate German work, post-traumatic ARF was ignored by the Allies[136]. There was some French recognition of uraemia after shock ((Duval and Grigant 1918; Richet and Flament 1918) which was not ascribed to kidney damage but

[135] I saw Him [Death] at Messina burying over one hundred thousand men, women and children under the falling houses in a single minute." Munthe, A. (1929). The Story of San Michele. London, John Murray. (p125) "…several thousand wounded lying among the ruins during two nights of torrential rain followed by an ice-cold tramontana, without any assistance whatsoever…" (p283)

[136] "This is no doubt one of the main reasons why the phenomenon seemed unknown to British physicians at the outbreak of the second world war." Brun, C. (1954). Acute Anuria. Copenhagen, Munksgaard. p16. For example, an early wartime review of shock in the BMJ makes no mention of the kidneys(McDowall, R. J. S. (1940). "The circulation in shock." Brit Med J **1**: 919-924.), and most later reports on battle casualties also make no (Porritt, A. E. (1945). Summary of Surgical Results (Forward Units). London, War Office.)or only passing mention (Porritt, A. E., R. K. Debenham, et al. (1945). "B.L.A. surgery." Brit Med J **2**: 377-382.)

rather to abnormalities of urea synthesis or amino acid production. Despite erroneous claims to the contrary (Eknoyan 2002), the British and Americans failed to recognise any metabolic consequences of severe battle injury. The influential report of the Medical Research Committee on Shock makes no mention of kidneys, urea, urine output or any of the other common consequences of severe injury, although it is detailed and accurate on the cardiovascular effects (Anon 1919).

This point has been laboured for several reasons, but mainly because it gives some insight into the importance given to precedence by academic clinicians. The sole 'history' of ARF, by a distinguished American nephrologist-cum-historian (Eknoyan 2002) makes several claims for the prior 'discovery' of ARF by Anglophone authors which cannot be substantiated by actual reading of the cited references. Specifically, Eknoyan credits AN Richards (later a distinguished American renal physiologist (Peitzman 2007)) with describing ARF in the MRC report on shock (Dale, Laidlaw et al. 1919). Actually, the clinical studies in which Richards was one of the assistants to the doyens of British physiology and a junior author of part of the final report, makes no mention of anything even remotely renal. These inaccuracies raise the question of motivation behind an ostensibly definitive review of the antecedents of the wider recognition of ARF. To the suggestion that retrospectively constructing a history provides a *post hoc* foundation establishing the credibility of that condition, must be added the possibility that such a created history might be manipulated to enhance not only the stature of the disease but also of individuals[137] and compatriots. This would appear to be in stark contrast to the studied neutrality and title to authority of 'scientific objectivity'(Daston 2001).

It appears that even in the German literature crush syndrome was regarded as a distinct entity, a feature of wartime trauma. That a common pathology and clinical course could follow a plethora of stimuli went largely unrecognised, perhaps because of the apparent infrequency of the condition. Thus the most influential textbook of renal disease and pathology of the early 20th century makes no mention whatsoever of ARF or its pathology (Volhard and Fahr 1914) despite the fact that its predecessor (Zeigler 1885) clearly describes and illustrates acute tubular necrosis. Unfortunately, the pathological entity is given three different names, is mixed up with a different condition (acute interstitial nephritis), and the prognosis is said to be good [if so, how was the

[137] "Authors sometimes collect (not select) references in an apparent effort to document their erudition, not their claims." Ingelfinger, F. J. (1974). "Why the citation?" N Engl J Med **290**: 855-856.

pathological material obtained?]. It would appear that, although hints at the existence of ARF were available, the disease fell out of medical recognition worldwide.

Bywaters initially did not make the connection between the renal lesions of the crush syndrome and the pathologically identical condition in other clinical scenarios, such as blackwater fever. This connection was, however, hinted at in the editorial which accompanied the first Hammersmith paper (Anon 1941), which appears to have stimulated the reporting of comparable non-traumatic cases, for example in obstetrics(Young and McMichael 1941; Young 1942). The conflating of such cases was the beginning of the formulation of ARF, but the compounding of disparate conditions into the concept of ARF was to come later, and not from the generally accepted sources.

The priority of precedence does tend to be distorted with time. Later authors may, sometimes uncritically, refer to intermediate publications, relying on earlier reviews or perceived 'key' papers to provide the original reference. Distortion of precedence also results from the, often subjective, selection of papers deemed to somehow be more significant or relevant than others, which might be equally deserving[138]. A case in point is the frequent citation (not only by American authors) of Lucke's 1946 paper published in a rather obscure journal (Lucke 1946) as the seminal work in which the disparate strands of ARF were pulled together into a unified syndrome. This is undoubtedly a major work, encompassing the renal pathology of more than 500 servicemen dying with ARF. Lucke emphasised and clarified the pathology and confirmed that some clinically identical cases could recover, although he reported mortality in excess of 90%. A distinct majority of his cases were related to shock and major trauma, not surprisingly for a wartime military pathologist. This might be thought to limit the applicability of his findings to the generality of ARF. He states that he has difficulty in incorporating 'medical' cases (such as patients with severe infections, sulphonamide treatment or poisoning) into his understanding of the ARF syndrome. In fact, Lucke muddied the

[138] The issue of citation bias is further muddied by the distortions imposed by the Anglophone publishing hegemony (Bottiger, L. E. (1983). "Reference lists in medical journals - language and length." Acta Med Scand **214**: 73-77.) and the 'scandalous' (Burnham, J. (1992). The *British Medical Journal* in America. Medical Journals and Medical Knowledge. W. F. Bynum, S. Lock and R. Porter. London, Routledge**:** 165-187.) parochialism of authors' selection of citable preceding publications (Velez, R. and D. L. Patrick (1982). "Citation of foreign literature in U.S. and U.K. journals." N Engl J Med **307**: 1155.).

waters by christening the condition "lower nephron nephrosis", a nomenclature that had but brief acceptance before being challenged as both inaccurate and confusing[139].

The synthesis of the clinical manifestations, pathology and multiple causes of ARF came not from the field of study of major wartime trauma (on which authors were justifiably focused) but from tropical medicine, as it were not only from left field but also, to make matters worse for later commentators, from British lateral thinking. Thus initially Foy and later more cogently Maegraith, Professor of Tropical Medicine at Liverpool (Foy, Altmann et al. 1943; Maegraith 1944; Maegraith and Findlay 1944; Maegraith, Havard et al. 1945), proposed that renal tubular destruction and consequent anuria or oliguria, almost inevitably leading to death, were the final common pathway for a plethora of clinical disasters including, but not limited to, trauma, burns, sepsis, malaria, obstetric disasters, sulphonamides, poisons, envenomations…the list is seemingly endless. That these authors recognised the commonality of the apparently disparate cases of ARF that had accumulated in the literature, must at least in part have arisen from their experience of 'medical' cases whereas the existing high-profile publications had considered only one specific area, albeit one at the forefront of attention because of the war. Maegraith's definitional synthesis was further reinforced by Darmady (Darmady 1947), whose role in the 1940s was later largely forgotten until resurrected by Cameron (Cameron 2007). These anatomical correlates of empirical clinical observations were, in a sense, a throw-back to the Parisian and German schools of the 19th century. They were, in Faber's terms, preparatory to a pathological-physiological way of understanding ARF: thereafter it was assumed that, whatever the antecedent cause, there was a common pathogenesis of the acute kidney dysfunction. This ontological unity dominated thinking and experimentation, despite the repeated observation of disconnect between the observed degrees of anatomical and physiological disorder. Further, the science of human ARF has been bedevilled by the absence of truly comparable experimental animal models.

Perhaps the most significant contribution of these authors was the concept that, with the possible exception of nephrotoxins, the cause of the pathological changes was, whatever the precipitating clinical mayhem, ischaemia (lack of adequate oxygen delivery) to the potentially critically hypoxic zone of the kidney at the corticomedullary

[139] "…a disservice to renal pathology in that it has added confusion instead of clarity." Bell, E. T. (1950). Renal Diseases. London, Kimpton.p276. "Jean Oliver famously commented of the title as 'euphonious, but erroneous'". Cameron 2002 p118, fn6

junction. This concept of "vasomotor nephropathy", as it was later called, has dominated clinical and experimental thinking about the pathogenesis of ARF ever since (Anderson 2001; Bonventre and Weinberg 2003; Molitoris 2003). Any debate and confusion over what ARF actually was was finally put to bed by a masterful paper from Boston, based on case reports, which clearly defined the clinical aspects, pathology, and management of ARF including, tentatively, the role of dialysis (Swann and Merrill 1953).

Thus far, this review of the concept of the disease or syndrome or symptom called ARF has, in common with every author who has considered the subject however tangentially, ignored ARF in the obstetric setting. Until a letter in *The Lancet* (Young and McMichael 1941), nobody had appeared to link the "new" syndrome of crush with what was a very well-known, if fortunately unusual, disastrous complication of obstetric mishaps, which would include puerperal fever, haemorrhage before or after delivery, abortion (by sepsis or because of the inducing agent, for example mercuric chloride), intrauterine fetal death, eclampsia, placental separation. That anuria was part of the subsequent fatal clinical course would have been well known but was poorly documented, perhaps because it was but one of many manifestations of a tragic circumstance. Obstetric ARF does not feature as a diagnosis in publications, departmental records, or later maternal health monitoring (Irving Loudon, to whom I am grateful for an enlightening conversation). Nevertheless, published reports from the late 19th century onwards (Bradford and Lawrence 1898; Griffith and Herringham 1906; Jardine 1906; Klotz 1908; Jardine and Teacher 1910; Jardine and Teacher 1910/1; Torrens 1911; Jardine and Kennedy 1913; Rolleston 1913; Glynn and Briggs 1914/5; White 1918; White 1918-9; Jardine and Kennedy 1920; Crook 1926-7; Bowes 1933-4) described the post mortem pathology of what appeared to be a uniquely obstetric kidney disease: acute bilateral renal cortical necrosis.

It gradually became apparent that not all of those with postpartum anuria died; some clinically indistinguishable cases were equally ill, but only temporarily so and recovered after a few days without urine output but with "toxaemia"(White 1918; Wilson 1922; Osman 1928; Scriver and Oertel 1930; Wakeman, Morrell et al. 1932; Gibberd 1936; Mach and Oppikofer 1936; McIlroy 1936; Dawbarn and Williams 1938). As these women did not die, there was no pathology to be obtained except if pieces of kidney were obtained at the time of surgery. The surgery was renal decapsulation, promoted as a "cure" for renal suppression and occasionally "successful" in these less severe cases(Jaffrey 1900; Harrison 1901; Dukes 1904; Edebohls 1904; Harris and Clayton-

Greene 1911; White 1918; White 1918-9; Bancroft 1925; Kellar and Arnott 1933; Abeshouse 1945; Reid, Penfold et al. 1946; Culpepper and Findley 1947; Bracey 1951). Thus, by the time Bywaters reported his "new" disease, obstetricians were aware of an analogous condition. Fatal cases of acute tubular necrosis, not cortical necrosis, had been described (Hadley 1902; Parkes Weber 1909; Suzuki 1912; Evans 1913-4; Young 1914; Parkes Weber 1921) and the management of oliguria associated with pregnancy appeared in obstetric texts (Dieckmann and Kramer 1940). All that was required was the crossing of specialist boundaries to share and compare experiences. Purists might argue that pregnancy-related ACN is a special case[140], perhaps differing in pathogenesis from ARF, perhaps only differing in degree. This however is to miss the point: obstetricians had accumulated a case-based experience of acute renal injury, not all of which had a fatal outcome, in relation to (illegal) induced abortions and pregnancy disasters. What did not happen was the transfer of this knowledge to the wider medical world, probably because of professional compartmentalisation, which must be the most obvious downside of specialisation.

The construction of the disorder called ARF in the middle decades of the 20th century coincided with the blooming of medical journals, certainly in the English language – new major journals appeared and the established ones expanded in size and readership. The role of journals in moulding 'modern' medicine has received little attention; in particular the exponential growth in volume of medical literature from the end of the Second World War which continues today and indeed has accelerated with the advent of electronic publishing. It is agreed that an essential criterion for specialisation is the establishment of a particular (usually organ-specific) literature, orientated specifically toward the specialty, as opposed to the generality of medicine or surgery. However, accepting that a specialism is, in part, defined by its literature begs the question of

[140] Acute cortical necrosis (ACN) may be conceptually regarded as the most extreme form of ARF, resulting from the same clinical causes, but is rare other than in association with obstetrics and some snake envenomations Chugh, K. S., P. C. Singhal, et al. (1983). "Spectrum of acute cortical necrosis in Indian patients." Amer J Med Sci **286**: 10-20, Chugh, K., V. Jha, et al. (1994). "Acute renal cortical necrosis - a study of 113 patients." Renal Failure **16**: 37 - 47, Prakash, J., K. Tripathi, et al. (1995). "Spectrum of renal cortical necrosis in acute renal failure in Eastern India." Postgrad Med J **71**: 208-210, ibid., Prakash, J., K. Tripathi, et al. (1996). "Renal cortical necrosis in pregnancy-related acute renal failure." J Indian Med Assoc **94**: 227-229, ibid.. Although there is tubular necrosis, the most striking feature is the (usually complete) ischaemic destruction of the outer part of the kidney, the cortex, from which there is little hope of recovery of renal function Evans, N. and E. W. Gilbert (1936). "Symmetrical cortical necrosis of the kidneys." Am J Path **12**: 553-560, Duff, G. L. and R. H. More (1941). "Bilateral cortical necrosis of the kidneys." Am J Med Sci **201**: 428-450, Dunn, J. S. and G. L. Montgomery (1941). "Acute necrotising glomerulonephritis." J Path Bact **52**: 1-16, Sheehan, H. L. and H. C. Moore (1952). Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage. Oxford, Blackwell Scientific, Rieselbach, R. E., S. Klahr, et al. (1967). "Diffuse bilateral cortical necrosis." Amer J Med **42**: 457-468.

whether the nascent specialty spawned its literature or whether, in fact, the appearance of an increasing volume of specialist literature within general journals was a prerequisite for specialty creation and recognition.

To take the specific example of renal disease, and in particular ARF, the British and European general journals of the 19th century contained occasional case-reports and reviews, the latter invariably based on publicly-accessible lectures to general medical or surgical associations. So, for example, Dreschfeld[141] in his Bradshaw lecture describes diabetic coma and includes a detailed account of the clinical and pathological features of ARF occurring in some cases (Dreschfeld 1881; Dreschfeld 1886). Lauder Brunton[142] described the tubular damage from mercury and other heavy metals in the Goulstonian and Croonian lectures of the Royal College of Physicians (Brunton 1887).This pattern persisted through the first four decades of the 20th century, with the addition of some physiological data as it was acquired. The publication of Bywaters and Beall's paper prompted an increasing number of reports and opinions, published in the major general medical or surgical journals, initially in response to the papers in the *British Medical Journal* and *The Lancet*, but increasingly related to the wider aspects of the specific subject. As the reports accumulated, the journals commissioned editorials, invited opinions and reviews, all of which swelled the mass of the literature. Thus, when medical publishing became economically more viable, and indeed profitable, at the end of wartime austerity, the ground had been prepared for the publication within mainstream journals of increasingly specialised clinical or laboratory papers. At the same time, especially in the USA, hugely increased funding of clinical science not only nurtured the production of new observations but also, critically, publication became an essential even the prime yardstick by which clinicians, clinical academics, and basic scientists were judged and assessed, and without which the continued funding of their endeavours became impossible. Publication in highly-rated journals became proof of a clinical scientist's worth and the criterion for support by grant-giving and appointing committees. Publications became increasingly mutually beneficial to practitioners and publishers alike, the latter then requiring reviews from perceived opinion-formers to accompany the original articles to contextualise them for, at that time, the predominantly generalised readership. The opinion-formers were, of course, also those who produced

[141] Julius Dreschfeld (1845-1907), Bavarian born Professor of Pathology and Medicine (1881-1907) at Manchester.
[142] Sir Thomas Lauder Brunton (1844-1916), physician at St Bartholomew's Hospital.

the original papers, so a self-propagating, self-fulfilling and self-perpetuating publication industry was formed. Ultimately, the productivity and arcanity of the specialist literature overwhelmed the general journals, creating the need for specialist journals, which themselves reinforced the identity of the specialties, and which were a business opportunity if the specialty was large enough.

The measurable consequence of these developments is that, in the field of ARF, publications grew from relatively infrequent in the 1940s to literally thousands by the turn of the century. The type of publication changed from clinical case reports, through synthesis of clinical features, to changing therapies, basic (animal) science, reviews and opinions. There are currently upwards of a thousand publications per year related to ARF in the English language (predominantly American) scientific and medical, both general and specialist, journals. Much of this output is supported by the continuing investment in academic renal research. But a remarkable proportion of this literary burden derives from reviews and opinions from a limited number of authors. If the number and length of such pieces is a measure of their significance then this work is, at least in the clinical sphere, now the leading area of publication. Perhaps because of the dominant position of American publishing, these opinion pieces follow a restricted and repetitive pattern: a small coterie of perhaps a dozen authors cover a limited range of topics. Perhaps through a perceived need to be 'cutting edge', the authors focus on promoting newer methods of treatment (Kelly and Molitoris 2000; Ronco, Bellomo et al. 2001; Kellum, Bellomo et al. 2003), any advantages of which have not been proven, speculating on the transition of animal experiments to clinical therapeutics (Molitoris, Weinberg et al. 2000; Molitoris 2003), or discussing the merits of the definition and reclassification of ARF (Mehta and Chertow 2003; Bellomo, Kellum et al. 2004; Molitoris, Levin et al. 2007). These topics reflect in part the changing management of ARF from an exclusively nephrological activity to one increasingly based in the intensive care unit, where responsibility may be taken over by a different breed of specialists: the 'intensivist'. The purpose of the published reviews may, therefore, be an attempt to maintain the centrality of the renal physician in this area of expertise, a 'turf war' which may have different implications either side of the Atlantic. Another common feature is their consistently positive tone: the application of laboratory science to newer therapies holds out the promise of untold

benefits in a condition with a continuing appalling outcome (Ympa, Sakr et al. 2005)[143]. But for the enthusiastic opinion-writers this outcome may not be so grim because the lack of definitional consistency of ARF or stratification of its sufferers means that comparisons across clinical series do not compare like with like, and that reclassification may show that things are not quite as bad as everyone believes.

The symbiotic relationship between journals and authors moulds the public face of medicine, but not necessarily the personal practice of medics. The publishing of weekly or monthly journals is big business; practitioners feel compelled to be seen to be 'up to date' by reading and quoting these journals and, indeed, the revalidation process for continued medical registration may in part be based on evidence of journal reading; aspiring academics must publish to gain recognition and grants; to be invited to write editorials or reviews is a measure of stature within academic medicine. This mutually beneficial relationship between commerce and academe cements the structure of the profession, especially the academic career progression, establishes leaders within specialties, and perpetuates the academic/service divide visible in some if not all specialties by placing a premium on new attention-grabbing, if unproven, research, opinion and therapy. On the receiving end are the public who, because all major journals have a highly polished system of press release to the general news media, constantly receive news of 'wonder cures' or exciting research uncritically presented without the necessary caveats or statistical doubts. Equally pressurised are the medical foot soldiers, increasingly obliged to demonstrate their familiarity with latest published evidence, yet inherently conservative and indeed dubious of innovation in their daily practice.

3.5 Whence Acute Renal Failure?

To further the exploration of disease concepts, their contingencies and consequences, I wish to consider more closely the history of the condition now generally known as acute renal failure (ARF). Professional historians shun the concept of biographies of disease (Cooter 2010) for a variety of reasons, not least because such 'life-histories' are predicated on retrospective diagnoses. Retrospectively locating past evidence of diseases as we now know them not only depends on projecting modern constructs or definitions backwards over time, but also makes the disease historically transcendent whatever its

[143] This analysis of published outcomes in ~16000 patients over 50 years shows that there has been no change in the mortality of ARF, which remains constant at about 50%. The possible reasons for this apparent lack of clinical improvement are complex and involve changing demography and disease patterns. The well-documented long series from Leeds plays a significant role in establishing these results.

past or present social and cultural contexts. In this view, professionals conflict with physicians or amateur historians, who tend to value the biographical approach as one way of understanding the present by tracing the route by which it was reached.

An attempt is now made to trace the history of what is called ARF by deliberately retrospectively testing past cases against modern diagnostic criteria. If the fit is more or less good, these reports can be used not only to trace the biography of ARF but also by so doing to give it a context, albeit primarily medical. Having repeatedly asserted that constructing ARF as a distinct entity was integral to the establishment of dialysis and nephrology, an attempt will be made to enquire how this construction was reached and how practitioners thought about it at different times.

ARF is a twentieth century disease concept with an apparently identifiable starting point, but in fact has a history in which it was seen but recognised differently. It is a disorder that illustrates the anomalies of disease-framing and in so doing may help to illuminate the conundrum of that framing. ARF is defined in the laboratory yet has dire consequences for the patient; without its technology it would not be much more than a medical observation but its technology would not have happened without the disease, each defining the other; originally defined in the laboratory, it became a major clinical problem, evolving later into a statistical aberration, the changes being driven by the availability of technology and changing awareness; from a rare clinical observation it became a relatively frequent problem, a consequence of both 'high-tech' medicine and lack of medical care; its existence influenced medical practice and public health policy; it created a major medical specialty; 'discovered' under very particular circumstances, ARF rapidly became a feature of every aspect of medical care and social behaviour. It is convincingly arguable that ARF is a 'bellwether' of post-war medicine, reflecting and marking its changes.

The history of the diagnostic category commonly known as acute renal failure[144] has yet to be written (Cameron 2002, p73). The framing of disease and the use of diagnostic

[144] A variety of largely descriptive terms were used for ARF, ranging from lower nephron nephrosis and acute tubular necrosis (both reflecting the morbid anatomy of the kidney) to simple symptomatic descriptions such as acute renal insufficiency or acute suppression of urine. Perhaps the best known alternative name was 'the crush syndrome', coined by Bywaters and Beall in 1941, which later came to be regarded as ARF consequent upon renal damage due to hypovolaemia and the release of myoglobin from traumatised muscle. As the understanding of ARF evolved, it was recognised that identical renal consequences arise from any cause of extensive muscle damage (rhabdomyolysis). The term 'acute renal failure' has been in common usage for many years (see Table 3.1) but is gradually giving way to 'acute kidney injury'; neither term is specific as to cause or mechanism and therefore conveniently covers the whole spectrum of clinical, pathological and experimental manifestations.

classification (nosology) has received attention in the historical literature (Faber 1930; Temkin 1977; Rosenberg and Golden 1992; Rosenberg 2002), but ARF differs somewhat from the 'usual' disease categories in that it is defined by a *functional* characteristic. That is, ARF has been, whatever its physical manifestations and irrespective of which of a constellation of potential causes is involved, defined as an abrupt deterioration of the excretory function of the kidneys, which is potentially reversible.

Although English-speaking authors give the impression that ARF emerged into the medical consciousness in the 1940s, it has a much longer traceable history. Ischuria, the cessation of urine flow followed by coma and death, was a well-recognised albeit uncommon mode of death before it was included by Giovanni Battista Morgnani (1682-1771) in his magisterial *De Sedibus et Causis Morborum per Anatomen Indigatis* (1761). If the previously offered definition may be retrospectively applied, the British literature of the early 19th century contains complete and clear descriptions of the clinical features of what is now called ARF:

William Heberden (1710-1801): "Extreme restlessness, and sometimes lethargic stupor, accompanies an ischuria, together with vomiting, hiccup, fever…A total suppression has lasted seven days and yet the patient has recovered. It has been fatal so early as on the fourth day. But in general those patients, who could not be cured, have sunk under their malady on the sixth or seventh day." (Heberden 1806 [1782])

John Abercrombie (1780-1828): "The disease seems, in general to come suddenly. The peculiar symptom is a sudden diminution of secretion of urine, which soon amounts to a complete suppression of it. The affliction is probably first considered as retention; but the catheter being employed, the bladder is found to be empty…after several days, the patient begins to talk incoherently, and shews a tendency to stupor. This increases gradually to perfect coma, which in a few days is fatal. The occurrence of coma may be expected about the fourth or fifth day from the time when the secretion of urine becomes suspended." (Abercrombie 1821)

Robert Christison (1797-1882): "When suppression of urine takes place suddenly…ere long there is languor, restlessness, vague general discomfort…attention is probably called to an excessive diminution or total suspension of urine…at length drowsiness comes on, generally in the course of the 3rd day; at about the same period or sooner puffiness of the features is observed…the drowsiness gradually passes to coma, which is usually formed on the fourth day and death ensues within 3 days more…in

some cases suppression appears to be commonly caused through…poisoning…" (Christison 1840)

This collecting of cases, by what Faber thought of as the British tradition of clinical observation, received the addition of pathological correlates later in the 19th century as microscopic histology developed. Thus, for example, Delafield[145] in a paper read to the Medical Society of New York carefully separates "parenchymatous inflammation or degeneration" from other types of "acute Bright's disease". He identifies the pathognomonic feature of ARF (necrosis of the renal tubular epithelium) and correlates this with a rapidly fatal course complicating extensive injuries, severe infection or poisoning (Delafield 1888). He further suggested that the same process may occur in milder cases who recover. At about the same time, Dickinson[146] reviewed acute suppression of urine due to "tubal nephritis" and catalogued amongst the potential causes most if not all the antecedents commonly recognised today (Dickinson 1885). This knowledge was also included by Sir William Osler in his authoritative and widely-used textbook (Osler 1892). There were even occasional cases scattered in the literature in which recovery followed intervention: for example, at Leeds a patient developed anuria following a cholecystectomy by Lord Moynihan and was successfully treated with intravenous saline (Braithwaite 1910).

Retrospective review may induce a tendency for criticism of previous generations of practitioners: that they somehow 'failed' to recognise and understand a particular condition. For ARF, this would be inappropriate. Before the middle of the 20th century the medical profession was not ignorant of or uninterested in acute anuria. They perceived it as an unusual occurrence, as but one manifestation of a complex and overwhelming clinical event. In the absence of effective drugs, sepsis was often rapidly fatal. Lack of availability of fluids (including blood) and the means of readily delivering them meant that shock was untreatable. Consequently, the most severely ill were liable to die before they could demonstrate the full-blown syndrome of ARF. Added to this, physicians lacked the tools later deemed necessary to establish the diagnosis. Rarity, complexity, therapeutic nihilism, and technical limitations all conspired to make ARF something of a curiosity among the plethora of life-endangering conditions with which they were faced. There is, however, an indication from the published works that those

[145] Francis Delafield (18411915), Professor of Pathology and Practice of Medicine, Columbia University College of Physicians and Surgeons, New York.
[146] William Howship Dickinson (1832-1913), physician to St George's Hospital and Great Ormond Street.

who did address the problem were also constrained by the prevailing approach to the understanding of disease. That is to say, the late 19th and early 20th century search for the cause of pathological change which resulted in clinical events. This manner of thinking had proved fruitful when framing infectious diseases or, later, endocrine disorders. Contrarily, the modern conception of ARF relegates aetiology and pathology to supporting roles in its construction, which hinges on measured function.

The story of the recent development of the concept of ARF, beginning with its rediscovery in 1940, is not only central to the history of nephrology and its technology, but is also relevant to the broader conceptualisation of disease. Here is a disorder in which the patient, although desperately ill and liable to die, has no specific symptoms apart from reduced or absent urine output. A disorder without a specific 'cause', but which can arise in a variety of circumstances, almost invariably secondary to a major clinical event but sometimes following something as relatively trivial as the ingestion of a commonplace medication for a minor ailment. This is a disorder defined by the laboratory and the physician, the diagnosis dependent on the demonstration of abnormal blood biochemistry which has, in the laboratory-physiology tradition of medical science, been agreed to be representative of kidney failure. This focus on technical problems with potential technical solutions excludes alternative ways of framing disease (Plough 1986). Even for an apparently established disease such as tuberculosis the post-war application of new medical technologies and investigative methods resulted in a reframing of perceptions with reference to its epidemiology and, most particularly, public and professional attitudes and behaviours (Hardy 2003). The new availability of effective therapy was a potent stimulus for the reframing process by propelling disease identification and, by destigmatising a disorder perceived as fatally incurable, greatly expanding the pool of individuals in whom the diagnosis was both recognisable and acceptable. The repeated reframing of tuberculosis unleashed changing behavioural and conceptual consequences (Condrau and Worboys 2010).

That ARF diverges from the traditional construct of disease diagnosis (an identified or speculated cause → discrete symptom cluster associated with diagnostic pathology → diagnosis → treatment (effective or not) → predictable outcome or prognosis) might partially explain the apparently anomalous observation that this dramatic illness

(event→oliguria→death) received little if any clinical notice[147] until the era of mass casualties in World War II. Prior to the description of the crush syndrome in survivors of the Blitz and the subsequent rapid global recognition of ARF, those with the condition may have been "a rather rare and motley group" (Cameron 2002, p110). The infrequency of the condition, spread across the entire width of medical practice (surgery, obstetrics, medicine) militated against its perception as a unified syndrome, this difficulty being exacerbated by the emphasis being almost entirely on the absence of urine rather than the entire physiological package now considered to constitute ARF[148], recognition of which later allowed a drawing together of the disparate clinical threads. Further, the suppression of urine output was considered to be a complication of specific causes, whether that cause be an obstetric accident, shock, poison, etc. etc. So the renal failure was pictured as a symptom peculiar to its antecedent event and not as a particular clinicopathological process independent of its precipitant.

3.6 Recovery of renal function

The ability of the kidneys to recover normal function after total failure became the cardinal feature of ARF. The possibility of complete recovery is the motivation for treatment of this complex condition; the understanding is that resumption of kidney function is the *sine qua non* for the patient's survival and eventual restoration of normal health. The potential for recovery defines acute renal failure. Further, if the kidneys did not possess this ability to reverse the period of total dysfunction, the temporary support of life by dialysis would be futile and the treatment would be considered worthless[149]. However, the period through which the kidneys fail to function may be too long for the patient to survive unaided. Renal recovery only became a realistic and frequent prospect if there was a way to sustain life during failure, and that way proved to be dialysis. It is relatively easy to trace the functional and pathological descriptions of ARF through the clinical literature, but identification of the point at which recoverability was realised is rather more problematic. Unless a disorder has been framed in terms that can enter and

[147] "... how [was] acute potentially reversible…renal failure regarded by people in the nineteenth and the first half of the twentieth century? In truth, [it was] regarded very little…" (Cameron 2002, p3).

[148] "…the rarity of the cases, their rapid onset as emergencies …, the difficulty of full investigation in patients so gravely ill, and the difficulty of interpreting post-mortem findings in terms of living physiology and pathology of the kidney and of the true nature and cause of the intoxication produced by suppression of urine, all make the problem a very difficult one. The most striking and puzzling feature…is its rarity compared with the frequency of its apparent exciting cause." Cubitt, A. W. (1936). "The problem of anuria: a review of recent work on renal physiology, with reports of two cases." B J Surg **24**: 215-226.

[149] Thorn 1948, p141: "This concept of a self-limited disease is extremely important in approaching the problem of therapy."

become fixed in the general medical consciousness, the practitioners do not see it, they do not recognise that the individual patient has a definable condition. This recognition is the essential first step in a chain of actions which include therapy and prognosis. Thus the pre-1940 physician, surgeon or obstetrician faced with a critically ill patient would apply the general management of the day and have no specific reason to focus on the kidneys; the reduced or absent urine output might be noted, but the attendant would have no established point against which to reference its significance. Routine repeated measurement of blood biochemistry simply did not occur until decades later, so the critical clue to the problem was absent. Common sense or experience would suggest a grave prognosis, but should spontaneous recovery occur this would be variously ascribed to good fortune, good management or divine intervention. If the practitioner did not know that the problem was ARF, the significance of the recovery would be lost (and there would be no reason to report the case). Histological material was unobtainable from the living patient so that comparison with post mortem appearances, if recognised, was not possible except under exceptional circumstances.

Despite the denials of the post-1940 'nephrologists', the cardinal features of what is now called ARF, including the potential for recovery, were known but only in a sporadic disorganised fashion. The information that ARF could recover was not accompanied by an understanding; observation did not lead to knowledge. This intellectual disconnection is not surprising because the potential for recovery from (and the histology later seen to be characteristic of) ARF was a sub-text in surgical papers reporting apparently curative intervention. It had been observed at autopsy that the kidneys of patients dying with acute kidney injury (both ARF and glomerulonephritis) were often tense and swollen. The kidney has a fibrous capsule and a theory arose that this capsule restricted the swelling of the inflamed kidney causing raised intrarenal pressure and compressing the renal tissue, physically preventing its function. This logically suggested that the relief of the intrarenal pressure, by surgical incision or removal of the capsule, would result in the return of excretory function. The procedure of decapsulation, originating at the turn of the century (Harrison 1896; Harrison 1901; Edebohls 1904), enjoyed a remarkable period of enthusiasm (Reid, Penfold et al. 1946; Culpepper and Findley 1947; Shapiro 1948; Bracey 1951) despite the opinion of many commentators that adding surgical

insult to existing injury was counter-intuitive[150]. The reports of 'successful' treatment contain two crucial points: firstly that kidneys had the power to recover from ARF (despite the attentions of the surgeons) and, secondly, specimens of kidney tissue were taken at operation and these showed the characteristic appearances of acute tubular necrosis (Jaffrey 1900; Dukes 1904; Harris and Clayton-Greene 1911; White 1918; White 1918-9; Abeshouse 1945). The significance of the renal recovery was lost from the collective medical memory, along with the other scattered reports of ARF, largely because the advocates mistook spontaneous recovery for surgical success[151].

When attention was again drawn to acute kidney injury by the reports of the crush syndrome, the focus was directed towards the pathological features and hence, by definition, towards fatal cases. ARF was defined by its histology, which precluded the inclusion of recovered cases (Lucke 1946). There was a smattering of clinically identical but non-fatal crush cases (Blackburn and Kay 1941; Henderson 1941; Longland and Murray 1941; Maitland 1941; Bradley 1942; Scott and Rob 1947) in the British literature. Further instances of spontaneous recovery had been reported following obstetric disasters, transfusion reactions or blackwater fever (Wakeman, Morrell et al. 1932; Gibberd 1936; Younge 1936; Rendle-Short 1943). These cases were reported simply because of their rarity and ARF continued to be regarded as uniformly fatal, and it is not clear when the realisation of spontaneous recovery became generally accepted. Academically, the histological description was aligned with appearances of regeneration of the tubules (Oliver (1953)) and this with clinical recovery (Swann and Merrill 1953) in the early 1950s, but clearly the prospect of recovery had been clinically recognised much earlier. Yet this realisation was essential as the stimulus for therapeutic intervention, whether by diet or dialysis.

The potential for recovery is obviously highly significant for the patient and his attendant, but is also critical in determining not only what doctors thought about ARF, but also what they did about it. A rapidly and inevitably fatal condition discourages the enthusiastic espousal of therapeutic intervention. On the other hand, some prospect, however small, of recovery acts as a stimulus for medical intervention and, perhaps more importantly, innovative thinking and action. If the recovery can be reasonably expected

[150] The logical disconnect of the surgical approach to anuria was underlined by a report (Wattenberg, C. A. and R. C. Coleman (1943). "Sulfathiazole toxic nephrosis and kidney decapsulation." Surgery **14**: 570-573.) that unilateral decapsulation (as was often the practice) was followed by demonstrable diuresis from and full recovery of *both* kidneys. The irony appears to have been lost on the authors.

[151] "It is incident to physicians, I am afraid, beyond all other men, to mistake subsequence for consequence." Dr Johnson, from a review of Dr Lucas's *Essay on Waters* (1734).

to be complete, leaving no permanent deficit that could result in future disability or medical consequences that might limit life style or expectancy, then the interested professionals would feel an increased obligation to ensure that recovery. Further, complete restoration would be seen as validation for any therapy, no matter how costly or onerous, that might demonstrably facilitate that recovery. In the case of dialysis, the treatment was seen to be an unjustifiable failure when applied to patients with end-stage, non-recoverable, kidney failure. However, the proponents of dialysis were persuaded that the costs and risks of dialysis were vindicated when specifically used on those with a reasonable expectation of (natural) recovery, i.e. those with ARF. It is quite likely that milder cases with spontaneous recovery after a few days could well be have been missed clinically, relative oliguria only being detectable from meticulous urine output charts, which were not necessarily routinely kept. Nonoliguric ARF (which generally has a better prognosis) was only lately recognised (Vertel and Knochel 1967; Anderson, Linas et al. 1977; Diamond and Yoburn 1982; Dixon and Anderson 1985), and then only when regular blood biochemistry became routine with the advent of autoanalysers. Renal pathology was only available after percutaneous needle biopsy became generally available, having previously been obtained at post mortem and hence, by definition, not from survivors. Nevertheless, clinicians observed and reported cases which were identical to the fatal pathologised ones in all respects, apart from outcome. Although all the pathology-based series reported a mortality of ~100%, case-based evidence accumulated that mortality in ARF, although very high, was not necessarily inevitable, and milder cases were increasingly reported.

It is however clear that the distinction between recoverable ARF and irrecoverable CRF was frequently blurred. In retrospect it appears that the cases successfully managed with conservative measures were the milder non-catabolic ones for whom physiological control allowed time for spontaneous renal regeneration and recovery. But conservative therapy was soon recognised as inadequate for the increasing numbers of more severely ill patients (Taylor 1957), who were too ill to live long enough for the renal tubules to regenerate. Thus while the potential for recovery allowed dietary therapy to appear effective, conversely the treatment was seen to have failed if it did not support life until recovery occurred. The promise of a better outcome drove the efforts to maintain life until nature solved the underlying problem; this was the driver for those persisting with dialysis. Arguably, dialysis would have been still-born were it not for Kolff's patient #17, who had sepsis and sulphonamide poisoning and who, unlike the previous 16, had

the potential to naturally recover after her condition had been improved by dialysis. Whether the cardinal feature of the potential reversibility of ARF was clearly in the consciousness of the early users of dialysis is a moot point. On balance, it is unlikely: Kolff and others treated any available patient with (usually very advanced) renal failure, only retrospectively appreciating that their survivors had spontaneously reversible lesions. Conversely, without the technology these patients would not have survived. Deaths from ARF usually occur within 10 days, the proximate cause of death being the effects of biochemical imbalance, which is correctable by dialysis. It is worth reiterating the felicitous conjunction of a 'new' disease and a new technology, each to a greater or lesser extent requiring the other to become established as medical routine. Without ARF, dialysis would not have had a role and would certainly have been abandoned. Without dialysis ARF, particularly as it developed in the latter part of the 20th century, would have been untreatable.

3.7 Summary

The framing of ARF as a disease entity, its establishment and acceptance and its objectification of changing attitudes and practices mark it as a sentinel disorder of modern medicine. ARF came to general attention because it was a complication of a new type of warfare, mass civilian casualties in air-raids. The exigencies of war directed the medical gaze towards a condition previously little regarded, probably because it was rather uncommon and perhaps perceived as merely a symptom of an inevitably fatal medical crisis, a mode of dying not a separate entity. The agreed upon clinical and physiological definition evolved through an accumulation of case reports, an unravelling of a confused and confusing nomenclature, and the gradual recognition that the disorder had its own history, bringing together comparable cases to unite previously dislocated medical constituencies. Changes in practice followed the acceptance that ARF was the anomalous consequence of (partially successful) medical intervention which achieved survival from the initiating catastrophe only to allow the development of a dire complication. Seemingly perversely, ARF is the corollary of medical risk-taking and grew in incidence and significance as medical practice and patient demography changed through the latter part of the 20th century. Its short history illustrates the negotiated framing of disease entities but also throws up some anomalies which conflict with but nevertheless illuminate previous histories.

Table 3.1. Alternative Names for Acute Renal Failure

1760	Ischuria renalis (Morgagni)[152]
1852	Acute desquamative nephritis (Johnson)
1879	Renal inadequacy
1885	Tubal nephritis (Dickinson)
1888	Hysterical ischuria (Charcot) Parenchymatous degeneration of the kidneys (Delafield) Acute Bright's disease
1908	Burn nephritis
1911	Acute suppression of urine
1916	Desquamative tubular nephritis
1917	Vasomotor nephrosis War nephritis
1918	Toxic tubular nephritis
1923	Toxic degenerative nephrosis Toxic nephritis Necrotizing nephrosis
1932	Hepatorenal syndrome (Liver-kidney syndrome) (Helwig)
1934	Acute tubular nephrosis
1936	Reflex anuria
1937	Traumatic nephritis Acute nephritis
1938	Acute haematogenous interstitial nephritis Acute toxic nephrosis Extrarenal azotemia
1940	Transfusion kidney Haemoglobinuric nephrosis Cholemic nephrosis
1941	Crush syndrome (Bywaters & Beall) Pressure ischaemia Compression syndrome
1942	Traumatic anuria Compressive syndrome
1943	Acute interstitial nephritis
1944	Crush kidney syndrome Tubulo-vascular renal syndrome
1945	Traumatic uraemia
1946	Lower nephron nephrosis (Lucke)
1948	Shock kidney
1949	Acute uraemia Acute renal failure (I Snapper)
1950	Acute tubular necrosis (Bull)
1951	Acute renal failure (Homer Smith)
1954	Acute tubulo-interstitial nephritis (Brun)
1990	Acute kidney injury

[152] The Oxford English Dictionary dates the first published use of ischuria (or, in English, ischury) to 1675 for "difficulty in passing urine, due either to suppression or retention".

4. RENAL MEDICINE AND DIALYSIS IN POST-WAR BRITAIN

The intention of this chapter is to describe renal medicine in the post-Second World War British context. Attitudes and behaviours established in this period (c.1945 – c.1955) provided the backdrop to the reintroduction of dialysis into the UK. Those with an interest in the kidney were gradually coming together to formulate clinical practice, but two centres (the Royal Postgraduate Medical School at the Hammersmith Hospital, and Manchester) exerted most influence through publications and by virtue of prestigious appointments, such as to the Council of the MRC. To focus on the leading British opinion-formers is not to portray them as reactionary, as has been done by some later commentators. Rather it is an attempt to describe the efforts of clinician-scientists to adapt their physiological way of thinking to changing circumstances.

4.1 Introduction

The decade following the end of World War II has been largely ignored by the few social historians of renal replacement therapy in Britain, who give the impression that dialysis sprung fully formed in the post-1960 era of treatment of end-stage renal failure. Yet the period up to 1956, when dialysis was reintroduced into the UK, was not characterised by medical inactivity or lack of interest in the kidney, its disorders, and their management. It may be regarded as a time of transition between the old and the new, whether surveyed from any of therapeutic, scientific, organisational or attitudinal aspects. The histories of the profession, the disease and the treatment are inextricably entwined and each is, to a varying extent, influenced by national circumstance, the changing role of hospitals and methods of health care delivery, the gradual appearance of technological medicine, and the internationalisation of medicine.

It could be argued that there is always a transition period between old and new ways of doing things, and it is easy to portray such an interregnum as some kind of conflict between old established opinions and practices and radical new ideas. Although later writers have tended to depict the events in the narrow field of nephrology in such a way, the reality was rather more nuanced. Whilst it could be said that established opinion resisted new ideas and technologies, focusing solely on their difficulties and limitations, in fact there was then no way of knowing, except intuitively, what was the best or the least worst of the available options. For example, not only was the concept of the power of randomised clinical trials essentially unknown, but also (in the context considered here) such rigorous evaluation could not, and never has been, performed: a ‘new’ disease had been ‘discovered’ but its ramifications took time to be appreciated; a new therapy

had been proposed but its value was unproven, even doubtful; there was delay in the accumulation of experience by individuals and centres of the 'new' disease, probably because it was actually then rare. Nevertheless, rather than inactivity, there were coherent attempts to codify the new understandings and to optimise what was available in terms of therapy, and to refine and develop this therapy. In doing so, treatments such as decapsulation so illogical and counter-intuitive to later generations as to appear bizarre if not frankly harmful, were swept away. What cannot be substantiated is the implied criticism by later authors (for whom dialysis was established, accepted, familiar and obvious) that the medical establishment, by somehow delaying the introduction of dialysis, prevented a significant number of patients from receiving adequate treatment. Undoubtedly there were some who might have benefited, but it is hard to establish the numbers and severity of patients with ARF at that time. The later negative strictures might be justifiable when the new insights and practices of this period themselves became entrenched and hence retarded the adoption of the next set of practices and understandings. The post-war academic and conservative regimes drew what they considered useful from preceding practices. Ideas that were in their time innovative are superseded by other practices, but do not disappear as they become, to a greater or lesser extent, incorporated into newer behaviours or they reappear later in different guises. The later application of technology was, at least initially, seen as an adjunct or a refinement of existing, in its time 'new', practice which was absorbed almost totally into what is now portrayed as 'modern' practice.

Nephrology, or renal medicine, did not exist as a definable specialty in the UK in the period under consideration. The treatment of kidney disease was accepted to be but part of the activity of physicians, who were all generalists. Treatment was holistic, based on time-honoured traditions of regimen: diet, rest, etc.. Many academic centres were interested in metabolism and some gave prominence to renal physiology. Only in one medical academic department (Manchester) was the kidney investigated programmatically and even there the research differed little from that of non-clinical university departments, except insofar as they at times applied basic scientific techniques to patients. The clinical research was not necessarily applied to practice.

Interest in the failing kidney in the UK in the period 1945 – 1956 followed three strands: academic clinical physiological investigation; clinico-pathological observations on acute renal failure; and development of therapy, mainly conservative, which was the least of the interests. Clinical investigation of the kidney was most notably carried out by

Platt, Black and Stanbury in Manchester. At this time, Manchester was perhaps uniquely positioned among the provincial teaching hospitals in the influence of its professors and the emphasis on clinical science (Valier 2002). Clinicopathological correlates of ARF had gained momentum from the observations on crush syndrome at the Hammersmith (Bywaters and Beall 1941; Bywaters and Delory 1941; Bywaters 1944; Bywaters and McMichael 1953; Bywaters 1990; Bywaters and Beall 1998), where this interest was developed into physiological studies of ARF and its treatment by diet. British renal medicine did not exist in isolation from events elsewhere and in many respects paralleled worldwide thinking and activity. There was less emphasis on the technology of medicine than in North America, although even there dialysis was very far from universally accepted and conservative counsel prevailed in most centres encountering the uraemic patient.

The pursuit of the study of kidney function in academic centres will not be considered in detail, except insofar as it impinged on the clinical practice of what was to become the specialty of nephrology. This academic/clinical interaction mirrored that which occurred in the USA: much of the academic work was conducted in isolation from the bedside, and was rarely construed as science to be *applied* to a clinical scenario; conversely, apart from using knowledge of electrolyte disturbances and their effects, those employing clinical methods did not apply investigational 'basic' science to their therapeutic endeavours. The pathological collection of data on the natural history of ARF in a way bridged the gap between academia and pragmatism, for example by providing a unifying structural mechanism for kidney failure, but largely pursued anatomical studies independently of the other two groups. For the clinician, the mechanism of acute anuria was largely irrelevant except in as much as it allowed him to regard all such patients as essentially the same, irrespective of the precipitating cause of their ARF. For the clinician there were essentially three questions, no matter how complex the situation and irrespective of the variations in individual patients: what were the metabolic consequences of the failed kidneys? What practically could be done to ameliorate these consequences? Could the kidneys recover function and so enable the patient to be restored? For the academic physiologist, the morbid anatomical appearance of acute tubular necrosis presented dilemmas rather than answers: absence of urine meant that classic clearance studies could only be performed on recovering kidneys (the diuretic phase which succeeds the anuric phase) and other investigational procedures, most especially renal blood flow studies, produced results that appeared to contradict the

accepted pathological/histological mechanism of ARF. The situation within 'nephrology' may be seen to reflect the traditional disunited trinity of physicians, surgeons and pathologists, and lead to organisational and conceptual consequences that became embedded, most obviously in the persistent divide between academic physiologists and their dialysing brethren.

4.2 The Hammersmith Hospital

Clinical staff at the Royal Postgraduate Medical School at the Hammersmith Hospital, London, contributed to and greatly influenced early British renal medicine in three ways:

- the (re-)discovery of ARF in the crush syndrome affecting Blitz victims (Bywaters and others, 1941 onwards)
- the first use of haemodialysis in the UK (1946, Bywaters and Joekes)
- the development and promotion of the conservative management of ARF (Bull, Joekes and Lowe from 1949)

It may therefore be instructive to use the events at the Hammersmith to provide a framework for the understanding of renal disorders and their treatment in the UK up to 1956[153].

To understand the significance of the identification of the 'crush syndrome' it is necessary to recount the wartime circumstances of the Hammersmith Hospital and of EGL Bywaters (1910 - 2003)[154] in particular. At the outbreak of war the Hammersmith became a 400-bed casualty hospital but, because it was not in central London, it usually received casualties dug out of bombed buildings at a late stage (Booth 1989). Consequently the Hammersmith was more likely to receive survivors of prolonged compression injury than were more centrally placed hospitals. This selected group were the ones who developed the crush syndrome, astutely recognised and investigated by Bywaters. Following his publications, Bywaters created a MRC team (Bywaters, Sir James Walton a surgeon at The (Royal) London Hospital, and a driver) to visit every major bombing in the Home Counties and even as far afield as Yorkshire, Norfolk and Bristol. The intention was to document the early stages of this apparently new type of kidney damage and also how to prevent it (the administration of alkali in the form of

[153] In this I have been greatly assisted by conversations with the late Sir Christopher Booth, Emeritus Professor of Medicine RPMS, and particularly by extensive correspondence with the late Professor Kenneth G Lowe CVO, MD, DSc, FRCP, Emeritus Professor of Medicine, University of Dundee and formerly Physician to the Queen in Scotland. Ken Lowe was at the Hammersmith Hospital from 1947 to 1952 as part of the team lead by Graham Bull.

[154] Obituary. British Medical Journal 2003; 326: 1461

potassium citrate was then in vogue). Bywaters later told Booth that this exercise was largely unfruitful apart from the Bethnal Green tube tragedy (173 people were crushed to death on the stairs of the tube station on 3.03.1943 when attempting to shelter from a flying-bomb attack (Bywaters, Crooke et al. 1943; Anon 1945; Bywaters and McMichael 1953; Gregg 2001)). The MRC also established a Clinical Research Unit studying shock at Guy's Hospital, the unit later being evacuated to Newcastle[155]. When the MRC/War Office British Traumatic Shock Team was sent to the Italian front in 1944, Bywaters became director at Newcastle working on industrial injuries, but returned to the Hammersmith in 1945. By recognising ARF due to muscle crush injury, Bywaters set in train a programme studying shock, injury, and acute renal injury, coordinated by the MRC. In so doing he performed the first integrated studies of a specific clinical renal problem, an achievement summarised in a history of the Hammersmith (Calnan 1985) thus (p107):

> "Bywaters'…work united all the Foundation Departments in the first communal research project, and established a process whereby future Hammersmith research would be conducted…"

In 1947, Bywaters became Director of the MRC Rheumatism Unit at Taplow, but not before he had made a further significant contribution to British renal medicine. In 1946 he visited Kampen, Holland and Kolff gave him one of his original machines. Bywaters, with the assistance of AM Joekes (a distant relative of Kolff), initiated dialysis at the Hammersmith from October 1946, making them the third group in the world to perform clinical dialysis. Over the next year or so, 12 patients received dialysis but 10 died (the Hammersmith group did however demonstrate the usefulness of haemodialysis in severe salicylate poisoning).

4.3 Conservative treatment

After Bywaters returned to rheumatology, he was succeeded by Graham Macgregor Bull (1918 – 1987), who developed the studies on ARF and, at least initially, continued with dialysis[156]. Bull's group pursued two lines of enquiry: into the metabolic changes in

[155] Ludwig Wittgenstein was their laboratory technician.

[156] KG Lowe (letter dated 24.2.06) gives some insight into the situation at the Hammersmith Hospital: "Lying in the desert [in Egypt on transit back from service in India] one day waiting for demob I was reading the BMJ and saw an advert for junior posts at Hammersmith. I cabled my wife to apply on my behalf. Early in 1947 I arrived at Hammersmith – in some ways a 30 year old veteran with an independent outlook – but I had to start at the beginning again. I attended Bywaters' rounds (I admired him). Graham Bull had arrived [from Cape Town] about the same time and I got to know him casually…When that 6/12 [resident to Russell Fraser] was up I became one of the outpatient physicians and waited – but for what?

acute anuria and, not unconnectedly, the application of a dietary conservative treatment regime. This 'Bull's Regimen' dominated not only the management of but also the conceptual approach to ARF for a decade. Cameron and Peitzman, have strongly suggested that the conservative regimen, by reflecting the then attitudes of the medical establishment, was a key factor in the delay in acceptance of dialysis. The Bull regime (Bull, Joekes et al. 1949) was based on that promoted by JGG Borst in Amsterdam (Borst 1948) but, being even less palatable, had to be given by nasogastric tube. Apparently, if the patient, already nauseated because of uraemia, vomited the mixture, the vomitus was re-administered via the tube as part of the strict fluid and calorie control. The diet (Figure 4.1) provided a lot of calories, no protein and a restricted fluid intake. As Peitzman has noted (1997 p301), the regime developed directly from academic physiology-metabolism knowledge: tight fluid volume control, calories to prevent breakdown of muscle and other tissues (catabolism: a source of excessive endogenous nitrogen waste products, considered to be the cause of uraemic symptoms), strict protein restriction to reduce the nitrogen load, and absence of electrolytes to avoid potassium and sodium intoxication. The diet may have been disgusting, but was based on good clinical science and utilised available methods and materials. It was a treatment of its time and, arguably, the best available option. Diet was then the foundation of practice, every hospital having a comprehensive formulary to meet every medical eventuality. The Bull regimen was thus an appropriate application of the best available physiological knowledge and therapeutic armamentarium.

The indictment of the conservative regimes by later writers on the history of nephrology has perhaps been led by Drukker (Drukker 1989):

> "Both Borst and Bull were in their time and in their countries powerful and influential men. Both…disliked medical machines and strongly opposed Kolff's 'gadgeteering'."

He further records (p33) that Borst, his erstwhile superior in Amsterdam, "taught students that he never needed an artificial kidney and that the one he had [donated by Kolff] was stored in the loft of his department in a somewhat rusty condition…" this portrayal of Borst as anti-technology may have had some justification. In the discussion

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Then chance. We juniors were all friendly and would meet in a club for sandwich lunch and coffee. And so it happened that one day Jo Joekes asked me if I would be interested in joining him to work on the AK. Bywaters was leaving and Bull would be in charge. It meant 3-4 years of security of tenure if one showed research potential. Bull readily agreed. We became great friends."

on Alwall's presentation about dialysis at the landmark Ciba Foundation Symposium on the kidney in 1954 (Lewis and Wolstenholme 1954), Borst stated that there was no artificial kidney in Amsterdam [incorrect] and that it was his practice to reduce the circulating volume of fluid-overloaded patients by applying constricting cuffs around the thighs. He did, however, admit that his "results weren't as good as those of Dr Alwall's", but his attitude was endorsed by Sir Robert Platt (Manchester) who stated that "we have always used conservative therapy and I think always got away with it" (p236). The leaders of British and European nephrology were countering data with opinions unsupported by facts. (It is interesting to note that this Symposium, regarded by Cameron as a landmark in the development of British nephrology, was still even in 1954 devoted almost exclusively to physiology-metabolism with, apart from Alwall's contribution, barely any mention of treatment). Cameron (2002 p114) names Bull, Borst and Peters (in the USA) as "strong and influential advocates of conservative management of acute renal failure who opposed the introduction of dialysis as 'unnecessary'". Cameron later (p124) does make some concessions:

> "Bull's and Borst's attitude to dialysis was not so bizarre as might appear today: in the 1940s and 1950s…many cases of acute renal failure were from poisonings, mismatched transfusions, abortion or trauma in fit, young anabolic subjects. Such regimes had a good chance of tiding these patients over only a few days of oligoanuria."

He also cites an American paper published in 1949 (Muirhead, Vanatta et al. 1949) which he regards as having been highly influential and which was certainly much quoted in the subsequent literature in both the USA and elsewhere. They reviewed the published results of dialysis and noted the poor survival rates (including Kolff's latest results showing 6/16 survivors (Kolff 1949)), even allowing for publication bias. They emphasised the fact that ARF was potentially eventually spontaneously reversible and that many of the symptoms thought to be due to 'uraemia' in fact resulted from salt and water overload, which was usually iatrogenic. Whilst they accepted that the latter could be cured by haemodialysis, they noted that the procedure failed to prolong the lives of nephrectomised dogs despite removing urea. The authors contrasted all this with their experience of 23 survivors in 27 consecutive cases of ARF treated conservatively.

> "They thus begin by advocating this course of management strongly. Their arguments convinced many, and in several countries after initial enthusiasm for its use, dialysis languished for up to a decade." (Cameron 2002 p115)

Perhaps coincidentally or perhaps because of a general desire to take stock of a disquieting situation, several papers appeared in the American literature in 1949, each recounting experience of and problems encountered in the management of ARF. Isidore Snapper, whose influence in bringing dialysis to the USA has been underappreciated, in a comprehensive review (Snapper 1949) reported 2 survivors of dialysis at the Mount Sinai Hospital, New York, and found 28 others in the literature. He considered that both haemodialysis and PD were fraught with difficulty. Another paper from the same institution (Leiter, Kroop et al. 1949) reported 8 deaths in 17 patients, of whom 3 died from fluid overload on admission and 5 of 7 dialysed patients also died. However, dialysis was only instituted when the patients were in coma. The authors' comments illustrate the attitudes of the day: "…we were permitted to use the artificial kidney because the outlook seemed hopeless" (p164) and "…dialysis…use is fraught with danger at the present time." (p169). There followed a lively discussion from American opinion-formers: George W Thorn (Boston) advocated conservative methods but felt that dialysis "will be used from time to time in the more severe cases"; Jacob Fine (Boston) whilst acknowledging that ARF was "far more complicated than many people realize" went on to say that "…peritoneal irrigation as we presented it…should no longer be tried, because the danger of peritonitis is too great…I am not optimistic about peritoneal dialysis as a practical clinical method."; V Vermooten (Dallas) stated that the artificial kidney was "…subject to innumerable sources of difficulty which may actually prove deleterious…the method…is actually dangerous and not suitable for clinical application." The generally pessimistic attitude was still prevalent in 1953 (Vest and Kelley 1953) when dialysis (referred to as an "accessory treatment") was considered unnecessary not only because of its "inherent difficulties" but also because it had not been reported "in adequate number or in detail for proper scientific appraisal." (Incidentally, it is of interest that the reviews and debates on dialysis at the time appeared exclusively in urological journals). Interested practitioners worldwide were cautiously and hesitatingly feeling their way through a challenging and complex clinical and therapeutic scene in which the role of mechanical substitution of renal function was very far from obvious.

Peitzman (1977 p301) ascribes what he sees as resistance to the introduction of dialysis to the natural conservatism of the medical profession allied to the influence of the clinician-scientists. He cites a 1949 editorial in the British Medical Journal as indicative of established opinion resistant to the introduction of technology. The tenor of

current medical opinion was certainly reflected this carefully argued anonymous editorial (Anon 1949) which accompanied Gordon Murray's report of his experience with his own machine in Toronto (Murray, Delorme et al. 1949). Murray's paper describes the design and manufacture of the machine, demonstration of its efficacy in urea removal in animals, and reports two successful cases (one septic abortion which "all agreed that her case was utterly hopeless", and a probable mismatched transfusion). Without giving any figures, Murray claimed that "there has been survival in about 50% of the patients treated. Those who succumbed were found on the whole to have had chronic kidney disease, and even though the purification of the blood was accomplished satisfactorily they relapsed into a uraemic state."[157] The editorial opens with: "In spite of much effort and ingenuity it is fair to say that the artificial kidney is still only an ideal and not an accomplished fact."

	Ingredients	KCal/Day
Borst's 'Dutch Gruel'	100g butter 100g custard powder 150g sugar 1.5l water	1750
Bull's 'Hammersmith Cocktail'	100g peanut oil 400g glucose gum Arabic water to 1l	2500

Figure 4.1. Conservative regimens for ARF

Further indicative passages include:

> "The principle is simple enough, but its translation into practice brings difficulties to the doctor and real hazards to the patient."
>
> "The dangers of the artificial kidney are admitted by its makers and users, but they argue that acute renal failure is so serious a condition that desperate measures may be justified. This contention is based on the assumption that acute renal failure carries a very grave prognosis, and figures can be found to support this view. Several critical surveys have lately appeared, however, which show that the high mortality of anuria

[157] An interesting footnote is provided by Murray's statement (p891): "the work was carried out independently of the University or other assistance." This is an indication not only of Murray's independent means, but also supports the view that he was something of a maverick, and that most if not all institutions were generally uninterested.

is largely attributable to faulty treatment, and that conservative treatment gives good results provided that excessive amounts of fluids are not given."

"Even more convincing is the experience of Bull and his colleagues at the London Postgraduate School, who have advisedly given up the use of the artificial kidney in favour of a high-calorie low-protein diet and a controlled fluid intake…They have had good results with this regime, and it can be carried out by those who lack the technical knowledge and fortitude to maintain a patient on the artificial kidney"

"It seems clear that until artificial kidneys become safer they have no place in the treatment of acute renal failure. To say this is not to suggest that the work done in this field has been wasted or that it should not continue."

Having established that there was widespread consensus that the value of dialysis was at best doubtful, the question remains as to how this determined events in Britain and the role of the Hammersmith in influencing the uptake of dialysis. Firstly, it is undoubtedly true that the use of the Kolff rotating drum dialyser was difficult, tedious, onerous and time-consuming (Figure 4.2). It is quite clear that Bywaters, Joekes and Lowe found its use burdensome. Professor Lowe gives a graphic account of his experience:

The Brigham modification of the Kolff rotating drum dialyser consisted of a stainless steel wire mesh drum, a Lucite hood with fog-lamps to demist, blood pump, and a heater. The Lucite hood prevented heat loss, and CO_2 or oxygen was given through the hood (to control pH). There was elaborate and time-consuming preparation for use: $2.4m^2$ cellophane tubing was wound onto a roller and boiled for 1 hour in a special steriliser. The tubing was then hand-wound round the drum, the ends attached to couplings which were in turn attached to the arterial and venous blood lines.100l of dialysate was prepared by hand, and had to be changed every 2hours. The blood path was primed with saline and tested with some of the patient's blood to look for foaming, an indicator of leakage. 6000 – 9000 units of heparin were given pre-dialysis. A venous blood pump (pulsatile, using compressed air) was used as a pump on the arterial (afferent) side would create too much pressure and result in membrane rupture. The patient's blood was allowed into the kidney in 200ml aliquots to prevent hypotension, or the circuit was primed with blood. A dialysis session would last 8 – 14 hours.

Figure 4.2. Procedure with Kolff rotating drum dialysis machine

"Dialysis for acute renal failure was a long day's procedure. The machine was set working using blood from the blood bank. It was important that the coils of cellophane tubing on the rotating cylinder did not leak into the fluid in the bath. Joekes was the expert on rotation couplings which he sealed with what looked like sterilised Vaseline (I always watched with suspicion). Blood from the patient (a pint at a time) was fed by gravity from a stand and passed through the rotation coupling to

the rotating drum and collected through the coupling at the other end and returned to the patient. I suppose we used both arms and cannulae in the veins. This was done for a good long time and seemed to involve a good many pints. Blood and bath fluid were monitored by the biochem lab. The patient had been heparinised and needed careful clinical watching. A patient with abdominal lesions might bleed (on occasion fatally). Infection was always a hazard. I can't remember the temp. of the bath fluid.

On one occasion the cellophane coil ruptured – the machine was switched off – the ends of the coil at the site of the rupture were clamped and an anastomosis made – and we carried on. The three of us kept going with black coffee. It was a time of meat shortage and Bull got a regular supply of biltong which he produced on these occasions. It was very salty. At the end of the day I might feel rather nauseated. Bull and Joekes came in early to start the procedure. I drove round the North Circular Road from Essex arriving about 9 a.m. B & J left in the early evening and I stayed overnight so that I could "clean up", check that biochemical monitoring was complete, and look after the patient. I could get a spare room and bed if need be. I remember one fatality at least (from fatal bleeding – abd. lesion)."

[*Letter dated 12.11.06*]

"I suppose I was not impressed by the prototype AK…Improving the AK would need engineers, chemists and technicians of a high standard. Having travelled in the USA I no doubt expected the AK would be improved there."

[*Letter dated 24.12.06*]

This experience is supported by a personal communication from Joekes (Booth 1985):

"It was a thankless task and Joekes remembers nostalgically "the full horrors of setting up the machine during the day and dialysing all night in an empty room on the north block using up to 2 grams of dry heparin to prevent clotting"." (p1773)

Bull in a letter dated 19.04.79 to David Hamilton (?) stated:

"The first AK was not without its troubles. Every patient developed rigors about 20 – 30 minutes after starting and the open bath which was kept at 37C was an ideal medium for the growth of organisms. Pinholes in the cellophane sausage casing used for dialysis caused troubles…"

Consequently it is not surprising that Lowe recollects:

"It was the time when the prototype AK was beginning to show all its defects. But we were getting a lot of cases of anuria referred to us and I would spend the next 3 years doing renal clearances, studying the cases clinically and taking up Bull's idea about

tube feeding a synthetic diet and generally getting a better recovery rate in our patients." [*Letter dated 24.12.06*]

The results with dialysis at the Hammersmith were depressingly poor: only 2 of 12 patients so treated survived. In part this was due to case selection: only 5 had acute disease and one moribund patient died one hour into the dialysis session. Nevertheless, the results could hardly have been seen to justify the effort of the dialysis procedure. They concluded (Bywaters and Joekes 1948) that "…in the uncomplicated case there is seldom need to use the artificial kidney." (p421).

In contrast, in Bull's first report (Bull, Joekes et al. 1949), 4 of 11 patients survived and recovered renal function on conservative treatment alone. In this series, all had ARF from abortion, mismatched blood transfusion or poisoning with mercury or other substances. They were thus previously healthy individuals with what could be considered to be the 'milder' end of the ARF spectrum. Nevertheless, all patients were reported as having oliguria of 7 – 21 days duration, meaning that they undoubtedly had established ARF. This difference in case-mix, demonstrating both increased sophistication in diagnosing ARF and an enlarged referral practice from which to select patients as suitable for intervention at an early stage, has been scathingly attacked by Cameron (2002 p124) who noted that Bull's results impressed the sceptics (such as the unknown author of the previously quoted BMJ editorial) "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." At least in print, Bull and his colleagues did not totally reject dialysis, although in practice they never again employed it. In the Lancet article (p233), dialysis is damned with faint praise:

"Dialysis methods have their dangers and difficulties, and we believe that, where this regime is started early, dialysis should not be undertaken. However, dialysis probably has a place in the treatment of the patient who is already in gross water, mineral, and nitrogen imbalance. Other methods of therapy, such as splanchnic block, spinal anaesthesia, and decapsulation of the kidney, are of doubtful value, and their use must be assessed against conservative management."

The Hammersmith ARF diet was developed to allow management of patients in preparation for dialysis. They had tried to use the Borst regime but this was so unpalatable that they could rarely administer more than 500 Kcals/day. Borst's 1948 paper is essentially a physiological study with a few illustrative examples, some of

whom did not have kidney disease (Borst 1948). According to Bull's 1979 letter, the development of the regime was influenced by (Sir) Francis Avery Jones, who "early on had realised the importance of fluid overload in causing death."

It may well be that the dietary regime of Borst and Bull was more radical than has been acknowledged. Although Peitzman concludes that it arose directly from the physiology-metabolism tradition, Borst in the introduction to his Lancet paper is at pains to demonstrate that established opinion was far from clear about the value of protein restriction and calorie supplementation. He quotes the 1943 edition of Cecil's Textbook of Medicine (the leading American reference) in stating that dietary treatment of kidney failure was of little therapeutic value ("effective protein restriction requiring such an increase in total calories that it is rarely feasible") and the doyens of American academic nephrology, Peters and van Slyke, who recommended that not only was there no need to regulate diet according to the level of blood non-protein nitrogen (≡ urea) but also that adults should have 1gm protein/kg/day[158]. It would appear that the conservative regimen rather than being a negative response to acute uraemia was rather a positive departure from existing treatments, if only insofar as devising a method of actually delivering a high-calorie, electrolyte-free, protein-free diet that could be demonstrated to have a beneficial effect on catabolism and fluid overload and which, in selected cases at least, improved patient recovery and survival. At the very least, this management did no harm, in contrast to the early forays into dialysis and previous treatments such as decapsulation, fluid challenge and potassium citrate. As Cameron says (2002 p113): "This conservative management was not simply doing nothing…", which is probably why "…influential individuals in several countries promoted this approach strongly", for example in New York (Stock 1952).

The long-term significance of the conservative regimen lay in its adoption by those treating acute uraemia, whether or not they were proponents of dialysis. Alwall, Kolff, Merrill and others incorporated Bull's regime, or something very much like it, into the total management of these patients. As individuals or hospitals gained a reputation for treating kidney disease, not only did referrals increase but patients were also referred earlier. As centres slowly became specialised, they had increasing numbers of patients who could be managed without dialytic intervention. Further, even in the most severely catabolic cases, dietary and fluid control reduced metabolic derangement, symptoms and

[158] Peters JP, van Slyke DD. 1946. Quantitative Clinical Chemistry, vol 1, pp 691, 698. 1gm protein/kg is about equivalent to a modern European middle-class diet, i.e. represents no protein restriction.

complications and hence reduced the demand for urgent and frequent dialysis. As will be seen, the Leeds group strongly advocated the incorporation of conservative measures in the total care of uraemic patients, and by doing so they and others achieved much more effective outcomes.

The lack of success with dialysis and the development of an attractive alternative treatment may have been sufficient to persuade the Hammersmith to either deliberately abandon dialysis or at least find little justification for its continued use, but other factors may also have influenced them. The HH was staffed by young clinical investigators whose career progression and interests were dependent on successful, that is to say publishable, research. It quickly became apparent that the use of the artificial kidney would not result in many publications and would become simply an onerous service chore[159]. The importance of clinical research and of scientific recognition through publication is a recurrent theme in the correspondence from Ken Lowe:

> "In those cases that came to us early we described the period of anuria, the early diuretic phase and the late diuretic phase. They could merge into each other but each had its dangers and different management. The Borst-Bull regime was saving lives and we wrote our Lancet paper [(Bull, Joekes et al. 1949)] in 1949 almost as an emergency, so that other medical units could experiment with it and reduce their mortality rates, hitherto in the region of 90%. More important was our paper in Clinical Science [(Bull, Joekes et al. 1950)] in which we gave the first clear account of the pathophysiology of acute renal failure in the group of cases to which we applied the name "acute tubular necrosis". We gave an account of our methods of assessing renal blood flow, glomerular filtration rates and tubular function. This was a finite piece of research that kept us busy from 1948 to about 1950. We then had to determine our future careers and research interests. [Lowe became a cardiologist and Professor of Medicine at Dundee; Bull and Milne were clinical physiologists and Professors of Medicine at Belfast and Westminster respectively; Bywaters became a rheumatologist; only Joekes remained within renal medicine.] We did not discredit the AK or even discard it. In the Lancet article we indicated conditions in which it might be used to supplement the Bull regime. The AK was left in the laboratory when we left." [*Letter dated 19.02.07*]

[159] Sir Christopher Booth *pers comm*. 15.10.2006.

Some indication of the experience, success and attitudes of the Hammersmith group may be obtained from their publications, which appeared up to 6 years after they disbanded. The group were firmly in the tradition of academic physician-investigators, regarding the accumulation of clinical data as their priority. What they retrospectively regarded as their most significant contribution (Bull, Joekes et al. 1950) is a classic of renal physiological investigation. The use of renal vein catheterisation, a notably invasive procedure of no therapeutic value, to study the oxygen consumption of the failing kidney was one of the rather numerous studies at the Hammersmith at that time which were vigorously attacked by Maurice Papworth (Papworth 1967) as potentially dangerous academic exercises performed for the benefit of the investigator rather than the patient, from whom fully-informed consent was not sought. One lasting useful piece of information from the *Clinical Science* paper was the description of the phases of ARF (onset, anuric or oliguric, early diuretic, late diuretic), or 'acute tubular necrosis' which they preferred in this paper, which became the basis for the clinical appreciation of the disorder when confirmed by a classic paper from Boston (Swann and Merrill 1953). Repeated clinical investigation formed the basis of a particularly relevant publication (Lowe 1952) which showed by repeated clearance studies up to three years after the episode of ARF (average follow-up of 679, range 201 – 1127, days in 14 female survivors) that "good clinical recovery, which is sustained, is the rule." This observation of the reversibility of a potentially devastating disorder with the restoration of normal health and activity (they reported subsequent normal pregnancies in three of their patients) was significant not only for demonstrating the remarkable regenerative capacity of the kidneys but also as justification for the time and effort expended on these cases, a potent argument for resources and a finding that was later shown to hold true for at least 30 years after the episode of ARF (Turney 1990; Turney 1992).

It is not possible to determine any publication bias that would have materially affected the results as presented – patient selection that may have resulted in atypically mild or severe cases. The impression gained from the reading of the clinical papers is that patients were predominantly from the mild-moderate end of the spectrum of clinical severity. There is a notable absence of sepsis or surgical or other trauma: these patients, which came to form the bulk of the later workload of renal units, have an intrinsically worse prognosis. But experience was accumulating that catabolic patients were unmanageable by conservative means alone, a realisation that slowly appeared in the literature. For example (Smith, Post et al. 1955):

"Experience with the relatively benign nature of acute renal failure in uninjured or uninfected patients should not be misapplied to those who have developed renal insufficiency in the course of extensive surgical or accidental trauma."

This was reiterated in the context of British civilian practice (Taylor 1957):

"The arachis oil/glucose regime of Bull et al. was usually poorly tolerated" (p704) "It may be concluded that, when renal failure follows head injury or surgical operations, conservative therapeutic regimes are generally ineffective…In such patients there seems to be a real need for an artificial kidney to keep the patient alive…" (p705)

In Taylor's series, only 5 of 31 survived and of these 26 deaths, 15 were directly attributable to ARF, rather than a combination of ARF and the underlying condition:

"The chief factor here was probably the failure of the conservative regimes to delay the advent of high blood-urea and serum-potassium levels until renal function could recover adequately." (p705)

The total number of ARF patients treated at the Hammersmith is never stated[160]. Lowe (1952 p1087) says that there had been 40 patients treated, of whom 26 survived. Later publications summarising the clinical details of specific groups total 67 patients of whom 26 died, among whom 7 had received dialysis (ie. only a minority of those treated in 1946-8 reappear in the later summary papers, which deal with specific diagnostic categories to the exclusion of others). Other papers, such as the 1950 study of the clinical physiology of ARF, only report 'illustrative cases'. The conclusion is inescapable that the Hammersmith either only treated or only reported patients in good prognosis groups. Thus of the 22 pregnancy-related cases (Bull, Joekes et al. 1955), 4 had acute cortical necrosis and died from irreversible renal failure. Of the remaining 18, 10 were oliguric for between 0 and 2 days. That is to say, their renal failure was transient, often amounting to little more than a biochemical perturbation. The other late reports likewise contain a significant proportion of mild cases, which might be expected to recover with or without any specific treatment.

Bull and his co-workers, in their publications, rigidly held to the view that the dietary regimen was the sole appropriate treatment of acute anuria. It is noteworthy that throughout they refer to their treatment as "rational". This reinforces the physiologically scientific rationale but also condemns alternatives as irrational. Thus in reviewing their experience with transfusion-related ARF (from mismatched blood etc.) they report 10

[160] In 1952 Bull wrote that he had seen 112 cases since 1947. Bull, G. M. (1952). "Discussion on the treatment of anuria." Proc Roy Soc Med **45**: 848-850.

deaths in 18 patients (Bull, Joekes et al. 1957), but seek to justify these results by "…but at least 5 of these deaths might have been avoided (some of the patients were seen before rational conservative treatment became widely accepted in this country)." (p116). The promotion of the dietary regime is a constant theme: "If rational treatment is applied, renal failure should rarely cause death." (Bull, Joekes et al. 1956); "The additional use of dialysis (particularly the modern highly developed artificial kidney handled by an expert team) is occasionally indicated but its routine use is controversial." (Bull, Joekes et al. 1955) "It is now possible to approach each clinical case with some optimism and rational methods of treatment and with the continued hope of furthering knowledge by clinical and biochemical investigation." (ibid pp 1155,1156). It is noteworthy that Bull continued to promote his dietary regimen as late as 1958 (Bull, Joekes et al. 1958), that is to say after the American experience with dialysis had become well known, as well as that of the units in the UK, including Leeds (Parsons and McCracken 1958; Parsons and McCracken 1959).

The 1955 paper on pregnancy-related ARF shows that the Hammersmith group had realised some of the limitations of their regimen and modified it accordingly:

> "…we have departed from our original regime in several respects. Patients with very mild acute renal failure need practically no dietary restrictions…The original tube-feeding regime of fat-sugar emulsion is still useful for some patients." (p1155) "Tube feeding the fat-sugar emulsion is often poorly tolerated because of nausea, vomiting, diarrhoea, or retrosternal discomfort…we have gradually gone over to the use of intravenous hypertonic glucose infusion…" (p 1156)

Patients, especially the most ill, frequently found the Bull regime intolerable, a fact covertly acknowledged by the Hammersmith group in their 1955 paper, and more openly by others[161], who sought to administer calories by intravenous infusion, a technique increasingly used at the Hammersmith. There were at that time no commercially available administration systems for continuous infusion into the great veins (the only way to administer hypertonic glucose solutions is via a long line into the vena cava) so each had to be an *ad hoc* system inserted by a surgical procedure As was later shown (Abel, Beck et al. 1973), the conservative regime which supplied only calories resulted

[161] Russell, C. S., C. J. Dewhurst, et al. (1954). "Prolonged anuria: Successful management by continuous infusion into the inferior vena cava." Lancet **1**: 902-905.: "In many cases this form of treatment, though unpleasant for the patient, is tolerated well and is successful, even though on occasion some of the emulsion may be vomited, when it has to be strained back into the intragastric drip. Repeated vomiting or diarrhoea is more serious…" (p904)

in overt malnutrition. This must, at least in part, have contributed to the prolonged 3-6 month convalescence of survivors (Lowe 1952). Although the fat element of the diet was quietly dropped, the regime was made even more unpleasant for the patients by the imposition of a draconian fluid restriction of 500mls per day (Bull, Joekes et al. 1955)[162], a move necessitated by the progressive fluid overload of anuric patients without the benefit of fluid removal by dialysis, due to an overestimation of insensible fluid loss (via the lungs and skin) and a late appreciation of the effect of water internally generated from the metabolism of glucose.

The various modifications of the conservative regime appear not to have been stimulated by a desire to improve its efficacy, but rather by a need to prolong the life of a concept that was only partially effective. If the Hammersmith group, and British medical practice, is to be indicted it must be for the persistent rigid adherence to a half-way treatment to the dogmatic exclusion of dialysis, the various methods of which were known and could have been made available. The use of the dietary regime as the sole treatment, as opposed to it being employed as an element of therapy integrated with dialysis (as was done by Alwall, Kolff, Merrill, Parsons), lead to two main problems particularly affecting the seriously ill: difficulty in administration and poor biochemical (and hence symptomatic) control, especially of potassium and urea. Indeed, Bull described a rare but devastating complication of prolonged high levels of potassium (muscle paralysis) without seeming to recognise the irony (Bull, Carter et al. 1953). Very soon after the departure of the original Hammersmith group, Milne and colleagues reported an upscaling of the conservative regime by the addition of potassium-reducing ion-exchange oral or rectal resins (Evans, Hughes Jones et al. 1953). As Cameron has noted, the selective use and reporting of the diet in relatively mild cases of ARF made it appear more efficacious than it perhaps deserved. The regime was an important step in establishing what Bull repeatedly called the 'rational treatment' of ARF. The error lay in the slavish adherence to the conservative regime, by the majority of those involved with such patients, to the exclusion of the use of dialysis for those patients who required it. This was the significance of Parsons' self-reported moment of enlightenment: the

[162] The patients suffered greatly from thirst. An anecdote from Leeds (Miss Freda Ellis *pers com*) recounts that when a nurse's attention was diverted, a patient drank the contents of the bowl that had been used for his neighbour's bed-bath. The severely restricted oral fluid intake also contributed to other complications that made the patients' lives even more miserable. A bone-dry mouth is not only unpleasant, it is liable to infection, and suppurative parotitis and oropharyngeal candidiasis were frequent painful complications, a significant factor in morbidity.

conservative regime was good but only insofar as it went; more was required – namely renal support by dialysis.

Conservative regimens, with minor local modifications, came to be used everywhere. Later generations derided this careful physicianly treatment when it appeared to be used to the exclusion of dialysis. It was, however, a logical application of traditional, and hence available, dietary practice to the most up to date physiological knowledge. Laboratory and clinical studies had shown the biochemical consequences of renal failure. This chemical mayhem seemed a reasonable explanation for the observed clinical manifestations. Laboratory studies had shown that the measurable consequences derived in part from dietary intake of protein and electrolytes and in part from internal metabolism. The intellectually satisfying therapeutic solution was therefore to restrict the intake of fluid, electrolytes and nitrogen. At the same time, and this is the critical point, the production of nitrogenous waste from metabolic protein breakdown (catabolism) was suppressed by a high intake of calories.

This physiologically elegant solution to what was seen as a metabolic problem worked quite well for some, but not all patients. The potential inadequacies of the conservative regimes became more apparent with the increasing numbers of complex cases. This increase, observed from the mid-1950s and accelerating thereafter, derived from changing practices. Supportive measures ensured that more critically ill subjects survived long enough to manifest ARF. More radical and adventurous surgery was performed on a widening age-range, the corollary being that more developed ARF. From this time on, those practitioners already primed by education or inclination to espouse technology felt an increasing need for additional treatment. The treatment on offer was dialysis. Despite the subsequent supremacy of dialysis over conservative therapy, the latter never disappeared. Metabolic control by dietary manipulation, unchanged in principle from that of Bull, remained the substratum of the management of uraemia to which dialysis was added. The principle of a high-calorie, low-protein diet was also applied to the management of chronic renal failure (Giovannetti 1985), and was a least partially successful despite in the long-term causing malnutrition. The Giovannetti diet was eventually abandoned when dialysis machines became more efficient.

Is it possible to be sure whether the Hammersmith group had a positive or negative influence on British renal medicine? Certainly they found dialysis to be both difficult and potentially dangerous, and remarkably ineffectual in terms of patient survival although this was due in no small part to poor patient selection. The impression I have

from Professor Lowe is that they were not anti-dialysis, but rather felt that it was a procedure whose time had not yet come. Lowe's recollections give a different perspective to that offered by the later nephrologist-historians:

"Prof McMichael was pleased that the Kolff kidney was being used experimentally in Hammersmith Hospital and gave a talk about it on BBC radio during the time I was there…The Kolff AK was still in use and I participated in its use in some desperately ill cases…It was about this time that Bull and Joekes were expressing doubts about the clinical usefulness of this prototype AK and considering the dangers of dialysis. The mystique and glamour of the AK and the fact that as distinguished a physician as Bywaters had used it was the reason for cases of acute anuria to be referred to us from London undergraduate teaching hospitals and from regions outside London. These peacetime cases were very different from wartime traumatic cases of anuria. We were able to identify common causes of mismanagement such as:

1. Forced fluids and other causes of fluid and electrolyte imbalance
2. Administration of potassium citrate
3. Decapsulation of the kidney and other surgical procedures meant to initiate diuresis.

In those cases that came to us early we described the period of anuria, the early diuretic phase and the late diuretic phase. They could merge into each other but each had its dangers and different management." [*Letter dated 19.02.07*]

"The success of the Borst-Bull regime in reducing the mortality from ARF by careful medical and nursing care and especially by advising against mismanagements common at that time was widely accepted. However it was also agreed that improved AKs might/would further reduce the mortality." [*Letter dated 6.03.07*]

"I don't think the Bull regime was ever considered an <u>alternative</u> to dialysis. By "conservative management of anuric uraemia" we proposed better clinical management as a holding operation. We were giving a clear account of the clinical picture of anuria or acute tubular necrosis, researching the pathophysiology…and presenting a method of management that would reduce the mortality considerably. The implication was that the prototype Kolff kidney required to be improved and problems of available antibiotics and heparinisation overcome. That would be accomplished where facilities and funding could be provided. For that reason Kolff went to the USA. Our two papers were well received and, I think, advanced the

understanding and management of anuria. The Bull regime, with or without modification, was widely used – by Kolff himself, Brun and others." [*Letter dated 12.11.06*]

"I had enjoyed my few years working on the kidney. I thought it important that we should document our early experience …I doubt if our conservative regime delayed development of the AK. It reduced the mortality in the anurias from c.90% to less than 50% meantime. Improvement of the Kolff AK and the development of other models was going on steadily abroad and such machines could be imported." [*Letter dated 24.12.06*]

There appears to be no reason to disagree with Lowe. They were struggling to understand a 'new' syndrome and, because of their training and inclination, pursued an investigational programme. The results of this were a contribution to the understanding of the physiology of ARF, successful career progression, and a therapeutic management plan which was not only beneficial to patients, being in their hands more effective than dialysis at least in selected cases, but also became generally incorporated into standard treatment if only as an adjunct to dialysis. Importantly, they diverted practice away from older, illogical and potentially harmful practices.

What became of dialysis at the Hammersmith? "The AK was left in the laboratory when we left" (Lowe 19.02.07); "…the machine was given to the department of surgery" (Booth 1985); "…for years it remained in the School workshop, a monument and a museum piece" (Calnan 1985). Certainly there was no further activity until 1957. After Bull's appointment as Professor in Belfast in 1952, he was succeeded by Malcolm Milne, who came from Platt's department in Manchester and was exclusively a clinical physiologist with no interest whatsoever in dialysis (CC Booth *pers com*). Milne and a urological surgeon, Ralph Shackman, visited Paris to see the Usifroid-Necker version of the Kolff machine, but after this was purchased in 1957, Milne took no interest in it and left dialysis to Shackman and the junior staff.

The hesitant acceptance of clinical novelty was not limited to dialysis but was also manifest in the 'official' reception of needle biopsy of the kidney. Percutaneous renal biopsy has been considered by the historians of nephrology to have been a key event in the definition of the specialty. This retrospective assessment was not shared by a rather hostile contemporaneous editorial in *The Lancet* (Anon 1955), which doubted whether sampling of the kidney would prove as applicable, widespread and useful as biopsy of

the liver. The author[163] did not share the optimism of the reviewed publications that biopsy would rapidly lead to a complete conceptual revision of renal disease.

4.4 Manchester

The academic department of medicine at Manchester (Valier 2002) probably had a greater influence on British opinion in relation to renal medicine than did the Hammersmith. This influence was subtle and derived not so much from published clinical studies as from the standing of two leading physicians: Robert Platt and his protégé Douglas Black (Cameron 2003). Both were academic physicians deeply immersed in physiological studies of the kidney. They were successively Professors of Medicine at Manchester; both became President of the Royal College of Physicians; and both held national influential advisory positions with the government and the MRC. Their eminence, political standing and acknowledged leadership in renal clinical physiology ensured that they were the first port of call for opinion pieces in the journals. Although editorials were conventionally anonymised, there is evidence that all those relevant to ARF and dialysis came from either Manchester or the Hammersmith. Platt and Black consistently demonstrated their clinical-scientific background and were cautiously conservative in their assessment of therapeutic innovations, seeking more evidential proof than was then available for new technologies. The Hammersmith renal group, as we have seen, were more overtly distrustful of dialysis.

Manchester and the Hammersmith appear to have had a virtual monopoly of opinion-forming in British renal medicine for almost two decades. Their consistent espousal of established traditional physiological investigative academic medicine, as distinct from the 'new' technological practice, can be traced through their publications.

"When anuria is diagnosed at its onset, conservative treatment should be all that is required to allow the kidneys to recover. This treatment, although properly called conservative, must not be thought of as meaning therapeutic inactivity; it is rational and demands attention to detail…" (Russell, Dewhurst et al. 1954). This statement is derived verbatim from an influential paper which, although it is the only foray into the clinical arena from Manchester, may be taken as indicative of the attitudes of 'academic' physicians (Black and Stanbury 1948). As the Manchester group were in effect the most significant in the field of academic renal medicine at that time, their comments must be seen as being the 'state of the art' and consequently influential, especially as published

[163] The review probably emanated from the Hammersmith as it inappropriately highlighted an elegant but irrelevant study by Milne of a vanishingly rare disorder.

in one of the two leading British journals. This publication is a thoughtful cogent argument on the pathogenesis and physiology of acute renal failure, but reflects the inadequacy of the available treatments. In reviewing the various theories of the cause of ARF, the authors conclude that "Suppression of urine has been observed in so many different disease states that it is doubtful whether the same underlying mechanism can be present in all." (p1103) In this the authors are at variance with the prevailing attempt to unify the theories of pathogenesis, but perhaps foreshadow concerns aired decades later. The comments on the attitudes towards ARF show a keen understanding of the reactions of the medical profession: "Although anuria is not a common emergency in medical practice it is an important one, partly because two of the commoner forms of anuria are iatrogenic and partly because persistent anuria is surely followed by death." (p1101); "The sudden occurrence of anuria after operation or transfusion may produce a mood of therapeutic desperation in which all sorts of procedures have been carried out from dry cupping to decapsulation." (p1102)

The authors review all available treatments, and demonstrate the inappropriateness of most: alkalis and diuretics are illogical because sodium sulphate (the favourite remedy at the time) cannot possibly work in anuria, mercuric chloride is toxic, and alkalosis is dangerous; they accept the advantage of diet to restrict protein catabolism but emphasise that the Borst diet is "remarkably unpalatable and would not seem to confer any corresponding advantage over a more varied diet containing about 30g of protein and 2,500 calories…" (p1103). Based on the work of Trueta (which was later discredited), it is recommended that renal denervation by splanchnic block or tetraethylammonium bromide might be useful in some cases. Of practical significance, they highlight the importance of infection control, and of restricting fluids and salt (to avoid "being pickled by excessive salt in the diet"). It is interesting that, despite being a well-recognised renal centre in a major conurbation, the authors are at pains to point out that ARF is uncommon in their practice, not only in the introduction quoted above but also in their critical review of treatment: "Since urine flow may be re-established quite spontaneously at any time it is impossible to assess the various possible methods of therapy by the usual method of considering their results, for no single centre is likely to encounter enough anuric patients to do a controlled trial of even one method of therapy." (This is of interest not only for its prescience in raising what remains an issue in nephrology, the absence of controlled trials in dialysis, but also for demonstrating that the concept of controlled trials was clearly recognised, at least by academic physicians, before the much

lauded trial of streptomycin in TB by Austin Bradford Hill, which is often cited as the first such study).

The paper does not dismiss dialysis out of hand, but reasonably cautions that "these methods are far from being generally applicable with safety…" They recognise the "…painstaking work of Kolff and Alwall in devising means of maintaining excretion during what is hoped may be a temporary suspension of renal activity." They recommend intestinal perfusion (dialysis), a "difficult" procedure of which they have some experience, and provide data on urea clearance by this method, whilst admitting it probably works by inducing profound diarrhoea causing "some discomfort to the patient." The Black and Stanbury paper has been considered at length because it appears to demonstrate, even at this comparatively early stage in the history of ARF, that the principles of pathology and treatment were well recognised, that opinion was not solidly anti-technology, that interested physicians were striving to improve management, and that ARF was still felt to be a rare condition.

A further theme elaborated by Lowe was the financial difficulties of the post-war period, both generally and in the hospital service in particular:

> "Very little clinical research was done in teaching hospitals. Hammersmith was almost unique. It had staff members with brains and energy but resources were meagre. We had a nurse/technician in the catheter lab and we got a BSc graduate Barbara Evans who learned to use the flame photometer. I wasn't aware of any technical/light engineering available to improve the AK." [*Letter dated 2.04.07*]
>
> "In the medical corridor in H.H. in 1947-51, I recall there were 3 labs on the left hand side and Sir John McMichael's office was on the right hand side…we had the AK in the 2nd lab. Eventually we got a building (? shed) at the back of H.H. for our kidney work." [*Letter dated 12.11.06*]
>
> "It is amazing that Hammersmith managed to do important research, especially on heart and kidney and liver, with modest resources. Britain was bankrupt after the war and still repaying Lend Lease. America was not a generous ally. The AK had to be improved where funding was available in rich countries." [*Letter dated 3.11.06*]
>
> "Poor Britain had sold its foreign assets and was bankrupt halfway through the war and dependent on the USA (Lend Lease) and Marshall Aid post-war – at a cost.
>
> Rationing was at its worst post-war. We all had a very cold winter 1947 (coal shortage). It was well into the 50s before there was much improvement." [*Letter dated 12.11.06*]

"A case could be made out for research funding to further develop the Kolff prototype in the UK wherever it would be of primary interest in a hospital that had technical help and possibly the prospect of commercial development. It was all a question of what priority should be given by funding policies. Perhaps too low a priority was accorded to dialysis in the UK in the early 50s. There was so much to be done in the post-war period that priorities had to be set and dialysis for some time had a relatively low priority." [*Letters dated 20.02.07 & 6.03.07*]

"I never foresaw the development of chronic dialysis and I didn't think much would be lost in waiting for the USA to make efficient AKs. Acute tubular necrosis wasn't all that common in peacetime." [*Letter dated 2.04.07*]

4.5 Medical Research Council and National Health Service

Lowe's view on Britain's post-war economic situation was undoubtedly shared by all who lived through that period of austerity. His views on expenditure on medical care and research are not, however, borne out by the figures. In particular, the MRC was the recipient of exceptional government largesse (Table). The official history of the MRC (Thomson 1973) records the following expenditure (Vol 1 p205):

YEAR	RECURRENT (£000)	CAPITAL (£000)	TOTAL (£000)	% +/-
1914/5	53.2		53.2	
1915/6	49.8		49.8	-6.5
1916/7	49.2		49.2	-1.2
1917/8	50		50	10.1
1918/9	54.6		54.6	4.6
1919/20	76	72.5	148.5	172
1920/1	125		125	-16
1921/2	130		130	4
1922/3	130		130	0
1923/4	130		130	0
1924/5	140		140	7.6
1925/6	135		135	-3.6
1926/7	135		135	0
1927/8	135		135	0
1928/9	148		148	9.6
1929/30	148		148	0
1930/1	148		148	0
1931/2	148		148	0
1932/3	139		139	-6.1
1933/4	139		139	0
1934/5	140.5		140.5	1
1935/6	165		165	17.4
1936/7	165		165	0

1937/8	195		195	18.1
1938/9	195		195	0
1939/40	195	70	265	35.9
1940/1	195		195	-26.4
1941/2	195		195	0
1942/3	195		195	0
1943/4	215		215	10.3
1944/5	250		250	16.3
1945/6	295		295	18
1946/7	415	50	465	57.6
1947/8	618	130	748	60.9
1948/9	770	365	1135	51.7
1949/50	1216	319	1535	35.2
1950/1	1363.8	290.8	1659.4	8.1
1951/2	1616.5	176	1792.6	8
1952/3	1505.9	181	1696.9	-5.9
1953/4	1671	135	1806	7
1954/5	1877.4	97.4	1974.9	9.4
1955/6	2097	88.1	2185.1	10.6
1956/7	2229.5	49.5	2349	7.5
1957/8	2775.5	37.5	3137.1	19.8
1958/9	3056.6	80.5	3137.1	11.5
1959/60	3445	81.2	3526.3	12.4
1960/1	4113	355.5	4468.6	26.7
1961/2	4862	808.6	5572	24.7
1962/3	5489	370	5859	5.2
1963/4	6524	509	7033	20
1964/5	8151	602	8753	24.5
1965/6	9637.5	450	10087.5	15.2
1966/7	11203.5	621.5	11824.8	17.2
1967/8	12542.9	1215.1	13758	16.3
1968/9	13358.2	1872.3	15230.5	10.7
1969/70	16393.2	1197.4	17590.6	15.5
1970/1	19486.8	1567.7	21054.6	19.7
1971/2	22260.5	1200	23464.5	11.5

Table 4.1. Medical Research Council expenditure, 1914 - 1972

The post-war period showed a marked enhancement of MRC revenue and capital investment. There was an 8-fold increase in the total budget during the period considered in this chapter. Medical research thus received considerable real-term increases each year, exceeding inflation and the rate of rise in GDP and exceeding that received by other government departments. Nevertheless, British medical research did not fare as well as in the USA: in 1954/5 the MRC budget was 0.0133% of the GNP, half that of the NIH in the USA where federal expenditure on medical research ran at 18-19 times that of the UK government or 5 times the expenditure/head of population.

The NHS, created in 1948, experienced even worse financial problems in this period. In part this was because the NHS had entered into an open-ended commitment with no basis for estimating or predicting costs (Leathard 2000). NHS expenditure remained constant at about 3.5% of GDP until the late 1960s (Rivett 1997), but inflation averaged 3.7% and the GDP increased at only half the rate of other European countries (Lowe 2005). Throughout the period, the British government experienced a series of economic crises on top of the persistent problem of repaying American loans: 1947 convertibility crisis, 1949 devaluation, 1950-2 Korean War, 1955 deflationary budget, etc. Additionally, construction of houses and schools was a higher priority than hospitals. Consequently there was minimal change in total NHS capital expenditure (Leathard 2000). The Guillebaud Committee (1953) raised concerns about capital expenditure, which was running at no more than a third of the pre-war annual level (Rivett 1997). The cumulative consequence of these factors was "shortage of equipment…British medicine had a worldwide reputation for good bedside care and clinical excellence; in the research field it was lagging." (Rivett 1997 p14)

The perpetual underfunding of the NHS was not directly relevant to renal medicine in the first two decades after the war. This will be considered later in relation to Leeds. Suffice it to say that the teaching hospitals retained a high degree of autonomy from 1948 to 1974, were directly funded from central government, and retained control of their endowment funds accumulated when they were independent voluntary hospitals. British renal medicine developed, and largely remained within, the teaching hospitals in the major cities: London, Leeds, Manchester, Newcastle, Glasgow, Edinburgh, etc..

4.6 Others

The Hammersmith group were not the only ones in Britain exploring dialysis in the post-war period. In March 1946 a urologist in Colchester, Ronnie Reid, performed peritoneal dialysis for two days on a woman with ARF due to mismatched transfusion. Reid and his colleagues were unaware of the scattered previous work on peritoneal dialysis and the key papers (Fine, Frank et al. 1946; Fine 1947) had yet to appear, and consequently worked from scratch – he used a Foley urinary catheter to access the peritoneum and a hypertonic saline solution as dialysate. Nevertheless, the patient survived, only the third in the world to do so with peritoneal dialysis (Cameron 2002 p99). A further five patients were treated over the next two years, and two of the three with ARF survived (Reid, Penfold et al. 1946; Reid, Penfold et al. 1947; Reid 1948). Meticulous biochemical measurements of blood and dialysate chemistry were recorded,

and Reid experimented with different dialysis solutions. Reid gave up in 1948, in part because of scepticism about its utility:

> "This is just a brief account of my experience with peritoneal dialysis, and the results are not impressive…Those undertaking peritoneal dialysis must be prepared to stay up all night. What have we gained from our experience?...There is no doubt that clinical improvement occurs which cannot be translated into statistical terms…in the modern treatment of uraemia peritoneal dialysis undoubtedly has a part to play. It should only be used in cases of temporary renal suppression when there is definite hope that the kidneys will recover sufficiently to maintain life, and it must be used with the greatest care for it is a dangerous procedure. It must not make the patient worse…peritoneal dialysis is a method in its infancy." (Reid 1948, pp 417-418)

Cameron (2002 p99) records being told that Reid gave up dialysis partly under the influence of the papers from Bull. One further point should be noted: Reid performed open kidney biopsies on two patients, probably the first ever renal biopsies in ARF.

The other individual involved in early dialysis was Michael Darmady (1906 – 1989), a pathologist in Portsmouth (Cameron 2007). He had encountered ARF in air-evacuated wounded from the invasion of Europe and demonstrated that the characteristic renal lesions also occurred in hypovolaemic shock without extensive muscle injury (Darmady, Siddons et al. 1944), thereby extending knowledge of the pathology of the condition, work which he continued later by microdissection of the renal tubules (Darmady and Stranack 1957). Before and after leaving the RAF, he experimented with artificial kidney design, having been made aware of Kolff's publication by a doctor from the Swedish embassy who wrote to him after his Lancet paper had been published. Darmady was assisted by "Mr Harrison of Goddard's Garage…the painstaking care with which they have constructed [from bits of wrecked aircraft] the many apparatuses used in this research." (Darmady 1948). He built a modified Kolff dialyser with an all-metal drum of different dimensions, pumps to control blood flow, and a canopy to reduce evaporation (thus anticipating the Brigham design modifications). He applied twice to the MRC for funding for the development of the artificial kidney and in his brief 1948 paper acknowledges a "grant for expenses". Apparently, he carried the machine in a trailer behind his car around hospitals in Hampshire. Darmady did not publish his results, but probably first used the dialyser in 1947 and treated at least 19 patients of whom at least 2 survived. He was clearly an ingenious man, designing building and using a flame photometer in 1949 after seeing a description of an American device. He realised the

need for the rapid and accurate assessment of fluid balance during dialysis and invented a weigh-bed, manufactured by WT Avery of Birmingham[164], which remained in general use for a long time. It is not known why he abandoned dialysis, but Cameron speculates that it was a combination of the enormous workload and personal commitment required. It is possible that he did not feel that the results justified the input. Darmady is today remembered mainly for his work on infection control, including establishing the first central sterile surgical supplies unit.

4.7 Professional associations

The existence of divisions between groups whose interest was directed towards the kidney is largely inferential, for example from what was written, ascribing attitudes and opinions which may or may not have been overtly stated. Recollections of participants suggest that these inferences may carry undue critical interpretation. An example of the situation obtaining at least until the late 1950s is provided by the professional organisation of those interested in kidneys. The inaugural meeting in 1950 of the British Renal Association, arguably the first national nephrological society, was attended by 27 founder members, of whom only 10 were clinicians: 3 physicians, 2 obstetricians, and 5 urological surgeons(Cameron 2000). 50 years later the membership was overwhelmingly clinical nephrologists, a minority of whom were predominantly 'academic'. Surgical members had disappeared, they having gained their own representation in urology or transplantation. Despite this change in constituency, which became apparent from about the mid-1970s, the meeting programmes remained at least half investigational science. This predominance of non-clinical publishing is reflected in the meetings of other national (particularly the American Society of Nephrology) and international societies and in nephrological journals. The early preponderance of non-clinicians reflected the situation in both the UK and elsewhere: there simply was no body of clinicians, particularly physicians, with either an interest or an expertise in kidney disease. The knowledge-base remained firmly in the laboratory, the province of the physiologist, with a few academic clinicians applying laboratory methods to an understanding of clinical situations ("the language of clearance, water and electrolyte balance, and acid-base disorders" (Peitzman 1988)), but not with the stated objective of applying this knowledge to therapy. This esoteric knowledge base "was a sophisticated comprehension of pathophysiology open only to those who cultivated it…" (Peitzman

[164] Darmady EM. 1954. Bed-weighing machine. Lancet 267: 689.

1988 p222). The bias in professional organisations resulted in a division between academics and artisan dialysis doctors which has been perpetuated in the USA, but which also had an impact in the UK (Cameron 2002, p185):

> [Of the UK Renal Association] "This body…showed a curious reluctance to discuss dialysis as part of its clinical and scientific 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."[165]

The antipathy of the senior members of the Renal Association towards dialysis was long-lived. Cameron records (2000 p21) that during the 1960s only 8 of 182 papers presented at the Association's meetings related to dialysis:

> "…members of the executive committee at that time recollect debates as to whether dialysis and related topics were '*a suitable subject for scientific discourse*'." "Thus the dramatic changes that took place in the field of dialysis during the 1960s in the United Kingdom were not reflected at all in the *research* meetings of the Association and at that time it was a purely scientific body."

The Renal Association was not alone in this attitude, as the divide between intellectual and practical nephrologists was, and remains, deeper in the USA. However, it is interesting that the key figure in this early confrontation with established opinion was Frank Parsons, at that time the leading but not the only British dialysis doctor. As Cameron states, the lack of enthusiasm for dialysis within the national society caused Parsons in particular to look to Europe, establishing in 1963, with William Drukker of Amsterdam, a register of patients treated by dialysis and transplantation (Parsons 1989 p1560) which evolved into the European Dialysis and Transplant Association (Drukker 1989; Disney 1998). In the USA, those interested in therapeutic technologies were excluded from specialist societies and so also established their own organisation: the American Society for Artificial Internal Organs. After apparently bitter disagreements, the national society accommodated the practical arm from about the mid-1990s. At more or less the same time, the EDTA officially expanded its remit (and as a token renamed itself EDTA-Renal Association) to increase its scientific content (Kerr 1989). (An

[165] Minutes of the Renal Association Executive Committee, October 1959: "Received a letter from Dr Parsons suggesting that a meeting should be devoted to a symposium on the artificial kidney. The Cttee rejected this proposal."

unintended consequence of this was a reduced appeal to nursing and technical staff, previously an important part of an inclusive association but now meeting independently).

The first symposium to be held on the artificial kidney was in Italy in May 1954 (Fogazzi 2003), where only 2 of 36 invited participants were physicians (both from the Hotel Dieu, Paris) and 33 were Italian surgeons, most of whom had built their own dialysers. This restricted field reflects the actuality of dialysis in Europe at that time: with the exception of Alwall in Sweden and two centres in Paris, there was essentially no dialysis apart from a clustering of surgeons dabbling in the procedure in Italy. The failure to adopt dialysis was, therefore, not a peculiarly British phenomenon.

4.8 Coda

In commenting on the Royal Society of Medicine section of Urology meeting at which Reid, Darmady and Bywaters presented their work, a Lancet editorial (Anon 1948) recorded the technical details without comment but concluded by endorsing Bywaters and "hoped that subsequent discussion and experiences will define more clearly the spheres of usefulness of diet, peritoneal dialysis, and blood dialysis." The Lancet had intermittent papers, letters and editorials on ARF throughout the post-war period, some of which give insight into current attitudes. Thus DAK Black (Black 1952) in a letter commenting on Oliver's work on the pathology of ARF wrote: "This new work does not detract in any way from the importance of conservative management of acute renal failure…" In 1954 (Anon 1954), an editorial divided the "syndromes of ARF" into four types:

- renal damage by specific poisons: good prognosis with conservative treatment;
- acute cortical necrosis: usually obstetric, poor prognosis even with conservative treatment;
- renal tubular necrosis: relatively good outlook with conservative treatment;
- extrarenal uraemia: good outlook with treatment of the underlying disease and appropriate fluid replacement.

The classification is arbitrary and essentially unhelpful for the management of ARF, and linguistically has the hallmarks of the Hammersmith publications. What is noticeable is that the anonymous author regards treatment as being exclusively Bull's regime. At the very end of the editorial, and quoting only a paper from the Necker Hospital Paris, the author writes:

> "But the good results of conservative treatment should not cause us to forget that there are some patients who need…infusions…and others who may have their life

prolonged towards possible recovery by the artificial kidney, or by peritoneal or other dialysis."

Thus, leading opinion had not changed in five years, and chose to ignore the results of dialysis from Boston, Paris and the Korean War, although one of the seminal papers from that war is quoted as showing the need for fluid resuscitation of battle casualties!

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5. ESTABLISHING DIALYSIS AT LEEDS

5.1 Introduction

The story of the establishment of dialysis at Leeds is inextricably entwined with the name of Frank Parsons. Although intending a career in surgery, Parsons' early path was somewhat anomalous as he specialised in physiological studies both as an undergraduate and as a surgical research fellow. This apparent contradiction of the traditional surgical and physicianly attributes has been frequently remarked in the early practitioners of renal medicine. His career shows a number of fortuitous events, the importance of personal contacts in spreading new technologies and procedures and, despite suggestions later made by Parsons himself, considerable tacit and active support from several individuals and institutions.

This chapter considers the situation in Leeds prior to 1956 which allowed the introduction of dialysis there, and the specific events building up to this event. It is a story of the actions of individuals in a particular hospital and administrative/financial setting (Turney and Pickstone 2011).

5.2 Sources

The sources upon which to build a history of dialysis at Leeds are somewhat limited. Leeds University Archive contains two useful collections:

- *Personalia/Parsons*: 9 boxes of papers, of which two are off-prints of published papers and five are transcripts of lectures given over many years to a variety of lay and professional audiences;
- *Personalia/Pyrah*: 23 boxes and large folders, some of which have been indexed and/or annotated by Pyrah himself. The notes are not dated, but appear to be personal recollections of events written after, and possibly long after, his retirement. Much of the archive consists of personal memorabilia, such as programmes of meetings and dinners attended, from a long and active career.

Parsons wrote a memoir, published in the British Medical Journal after his death in 1989 (Parsons 1989). That it was published shortly after his obituary had appeared in the same Journal was probably coincidental, as the memoir appears to have been held over so as to appear in the Christmas number. The obituary (Anon 1989) provides little useful information.

For personal recollections, I am indebted to Christopher R Blagg, Emeritus Professor of Medicine, University of Washington, Seattle and Emeritus Director, Northwest

Kidney Centers. Blagg was a key participant in two significant events in the history of nephrology. From 1958 to 1963 he was Lecturer in Medicine at Leeds, sharing the responsibility for dialysis with Parsons and providing the clinical medical care for the renal patients. During this time, amongst other contributions, he introduced percutaneous needle renal biopsy and published extensively. He spent time with Belding Scribner in Seattle when long-term dialysis for end-stage renal failure was starting, before moving permanently to Seattle in 1963, where Scribner and he established the technical, clinical, and ethical parameters of long-term dialysis. Blagg was a founder of the World Kidney Forum which is a group of nephrologists interested in the history of their specialty, remained in close contact with the various early participants in the Leeds story, and has published extensively on the history of dialysis, particularly as it relates to Seattle (see, for example (Blagg 1998; Blagg 2007)). I am indebted to Chris Blagg for his friendship and for his generous sharing of his own and others' recollections.

The evolution of the understanding of acute renal failure and the adaptation and application of dialysis at Leeds can be traced through clinical papers published in medical journals. A series of such papers will be used not only to map the progress of clinical practice in Leeds, but also to analyse alternative purposes of such publications: to advertise the authors' expertise, to champion and promote the new technology, to provide evidence of activity and achievement to influence paymasters and sponsors. In addition to clinical papers by Parsons and his colleagues, the present author has published on the "clinical history" of acute renal failure derived from the records held at Leeds General Infirmary (Turney, Ellis et al. 1989; Guly and Turney 1990; Turney 1990; Turney, Marshall et al. 1990; Turney 1992; Woodrow and Turney 1992; Woodrow, Brownjohn et al. 1995). These clinical records dated from 1956, making it the longest and largest series in the world (Cameron 1986). This unique and irreplaceable archive was destroyed by the management of the United Leeds Teaching Hospitals NHS Trust the day following the present author's retirement. However, preserved from this archive are 15 notebooks, meticulously kept by Mrs Shirley M Hobson between 1956 and 1971, when she was the biochemistry technician in the MRC Unit, and which contain clinical and laboratory data of all dialysed patients.

The records of the Medical Research Council, held at the National Archives, Kew (reference FD/1), contain correspondence with and reports from the Leeds MRC Metabolic Disturbances in Surgery Unit.

5.3 Administration and finances of Leeds General Infirmary

The General Infirmary at Leeds (hereinafter the LGI) was founded in 1767 and its history (Anning 1963; Anning 1966) mirrors that of most provincial voluntary hospitals in England (Poynter 1964; Woodward 1974; Pickstone 1985; Granshaw and Porter 1989; Carruthers and Carruthers 2005). The administrative structure and wealth of the LGI provided fertile ground for a small group of medical staff to embark on the therapeutic adventure that was dialysis. Prior to the many management reforms of the last quarter of the 20th century, the NHS was remarkably lightly administered. The institutional structure of the teaching hospitals was largely untouched when they were incorporated into the NHS (Webster 1988; Webster 1996; Webster 1998). The government assumed their running costs and the consultant medical staff received a salary for continuing their normal (previously voluntary) activity, but otherwise these prestigious hospitals were essentially indistinguishable from their pre-nationalisation voluntary days. They remained independent of the newly-created Regional boards and were funded directly by the Ministry of Health. In effect, these elite hospitals maintained their separate identities and the Boards of Governors acted as agents of the Minister (Webster 1988).

The LGI did not differ from other teaching hospitals in its institutional structure. The day to day running was in the hands of the Hospital Secretary (Mr J Arnold Tunstall) and the Matron ([Dame] Kathleen Raven from 1949 to 1957, when she transferred to the Ministry of Health and was replaced by Grace Watts). The Board of Governors selected its own members, apart from the co-opted representatives of the medical staff and the University. The Board was composed of local worthies, who often served for many years[166]. All were locally influential by virtue of wealth and position, many had national influence as MPs or in the Lords, and all had in common a deep commitment to the interests of the Infirmary. The Board oversaw the finances and policy and also confirmed appointments to the staff.

Throughout its history the Infirmary had been dominated by its medical staff rather than the lay Board. On occasion this led to accusations of a medical clique unfairly influencing decisions on, for example, appointments (Sagar, Mayne et al. 1864). All consultants were automatically elected to Faculty[167], the Chairman and another

[166] For example, the Lupton family were not only prominent in the legal profession and in Leeds politics, but also six members of three generations served on the Board of the Infirmary.

[167] It was no coincidence that from the late 19th century consultants were also elected to membership of the Leeds Club, a gentlemen's club a few minutes' walk from the LGI. Well-founded rumour had it that the

representative being members of the Board. Faculty ensured that the senior medical staff could present a united voice which the Board was consistently disinclined to challenge. The attitudes and interests of the Board and of Faculty coincided; both were deeply aware of the traditions and ethos of the institution, which itself remained essentially unchanged and autonomous until 1974. The consultants' views took precedence, the Board and its administration seeing themselves as enablers of medical policy. Faculty was traditionally independent of management and served to advise management (and, some said, to control it). It was highly influential in the hospital's decision-making process. It is interesting, from a modern perspective, to see from the records how deferential the Governors were to Faculty's opinion. This was the era in which hospital administrators were "supportive technicians" (Learmonth 1998), dealing with the administrative arrangements of support services.

The LGI was allegedly the wealthiest hospital in the country, after St Thomas's London. It is almost axiomatic in the extensive literature on the run-up to the creation of the National Health Service that the voluntary hospitals were in a parlous financial and physical state by 1939, when they were effectively rescued by the wartime Emergency Medical Service, the precursor to full nationalisation of the hospital sector in 1948 (Abel-Smith 1964; Pinker 1966; Godber 1988; Rivett 1997). This is, however, a London-centric view. The provincial voluntary hospitals, and the LGI in particular, were largely in balance or surplus (Powell 1992; Powell 1992; Cherry 1997; Gorsky, Mohan et al. 1999; Mohan and Gorsky 2001; Gorsky, Mohan et al. 2002; Mohan 2003; Cherry 2006; Mohan 2006). The London teaching hospitals were more dependent on investment income (30% ordinary income in London, 12 – 14 % for provincial teaching hospitals) and hence disproportionately affected by the Depression of the 1930s. Conversely, the provincial hospitals derived greater income from patient payments and contributory schemes. Of these, the LGI was particularly favoured: a strong and stable contributory scheme (The Leeds [Saturday] Hospital Fund), support from local manufacturers, continuing charitable support, a large modern wing for paying patients, an integrated medical school with the LGI forming the hub of the university campus. All the old voluntary hospitals were held in high esteem by the British public, and this attitude continued after nationalisation. Certainly great buildings and institutions are emblematic of civic pride and identity. Possibly this local approbation and feeling of ownership was

hospital's business was decided over lunch at the Club, and reported back to the Board. The Board eventually provided a subsidised exclusive Consultants' Dining Room within the Infirmary.

particularly well developed in Leeds. LGI was exceptionally successful at generating income from contributory schemes, as shown by comparison with Manchester Royal Infirmary and other provincial hospitals (table derived from Cherry 1997, p324):

Table 5.1. Ordinary Income from Works Collections and Contributory Schemes

	1900 - 4	1910 - 4	1920 - 4	1925 - 9	1930 - 4	1935 - 9
LGI	21	27	34	34	38	39
MRI	-	3	-	7	9	25*
PROVINCIAL TEACHING	10	16	19	33	38	41
ALL ENGLISH PROVINCIAL	18	22	25	29	29	30%

* Deliberate programme to increase workers' contributions (Valier 2005; Valier and Pickstone 2008).

The available charitable funds, controlled by the Board of Governors, for the period in which the dialysis machine was purchased are shown by: *The Eighth Report of the United Leeds Hospitals for the period 1st April 1956 – 31st March 1957* which includes (pp 52 et seq) the following audited accounts:

Endowment Fund*: Capital £958,145

Income £52,968

Donations/bequests to the LGI: £18,115.15.5

(Total hospital NHS expenditure for the period: £1,581,005)

(* Other large funds also existed, some with restricted applications)

Demonstrably, the Board controlled reserves greater than the actual running costs of the hospital which could be used at their discretion to cover any current account shortfall or for capital projects at a time when the NHS was unable to make any such investment (Cutler 2006). The fabric of the LGI was in good condition at the start of the NHS, having suffered little or no war-damage and because of investment by the Board, supported by public fund-raising. In contrast, much of the country's hospital stock was in poor condition, inadequate or even redundant and capital expenditure in the first decade or so of the NHS was at a third of the pre-war level (Cutler 2003; Cutler 2006). The special funding of the teaching hospitals, together with its charitable reserves, to some extent protected the LGI from the "almost permanent economic crisis" of the early NHS (Bridgen and Lowe 1998).

5.4 People

"In Britain, the modern, continuous era of dialysis for renal failure started in Leeds and Frank Parsons was entirely responsible." (Hamilton 1984)

1941	BSc (Hons), Physiology, Leeds University
1943	MB ChB (Hons), Leeds
1943-6	House Surgeon & Demonstrator in Physiology
1947-9	Graded Surgeon, RAMC
1949	Surgical Registrar to Mr L N Pyrah
1951	Research Fellow in Urologic Surgery
1954	American Cancer Research Fellowship, Chicago
1956-62	Assistant Director, MRC Metabolic Disturbances in Surgery Unit, LGI
1961	MD with distinction Consultant in Clinical Renal Medicine, LGI
1967	Director, Renal Research Unit
1971	Senior Clinical Lecturer, Leeds University

Figure 5.2. Frank Maudsley Parsons (1918 – 1989)

The individual who gave the most significant support to Frank Parsons was Leslie Pyrah. Indeed, the extant records might tend to the conclusion that Pyrah, rather than Parsons, was the prime mover in the establishment of dialysis at Leeds, although his name is rarely if ever attached to it. Pyrah was a highly successful general surgeon, specialising in the surgery of the genitourinary tract at a time when urological surgery had not yet been recognised as a surgical subspecialty. In 1950 it was decided among the surgeons in Leeds, and endorsed by the Board of Governors, that there should be a Department of Urological Surgery (possibly the first such in the UK) which Pyrah was invited to head. Pyrah records, and this is supported in Parsons' memoir, that he insisted that the department should have an active research programme, which he considered to

be an essential part of surgical training. He therefore established links with other departments, most successfully with Professor Spiers in Medical Physics, and raised funds from local sources. Throughout, Pyrah managed his surgical practice, research programme, fund-raising, and his local and national commitments from his private consulting rooms in Park Square, Leeds.

The key events in the pre-dialysis stage of the story are the periods of research spent by Parsons, under the direction of Pyrah, in both Leeds and the USA. His research at Leeds concerned the metabolic effects of reimplantation of the ureters into the colon following total cystectomy for bladder cancer. The consequent hyperchloraemic acidosis resulted from the differential reabsorption of urinary electrolytes by the colon, and was at that time a difficult physiological problem to unravel. (Parsons 1989):

> "Luck soon came my way for I acquired and operated the first flame photometer for estimating sodium and chloride concentrations to be installed in Yorkshire." (p1558)

What had previously been slow, laborious estimations of biochemical parameters had now become rapid, accurate and repeatable – an essential prerequisite for managing patients with severe metabolic disturbance such as kidney failure (Kohler 1982). In his memoir, Parsons understates the importance of potassium (Forbes 1995) and the crucial role of its rapid determination in the management of patients with renal failure. Indeed, as will be argued later, a raised blood potassium level was an important criterion for the contribution by the Leeds group to the management of renal failure (clear indications of the need for dialytic intervention). Although not realised by Bywaters and Beall in their classic paper (Bywaters and Beall 1941)[168], hyperkalaemia had rapidly been recognised as the primary cause of sudden death due to cardiac arrhythmias and standstill (Kolff 1950). Again quoting from Parsons' posthumously published personal recollection (Parsons 1989), his interests and biochemical expertise resulted in him being asked to look after patients with acute renal failure. However, he does not give an indication of the numbers of these patients, neither is there any documentary evidence of the source(s) from which they were referred. At that time, Parsons did not have his own beds at the Infirmary. The implication is that these patients somehow came to the Urology department because of the biochemical expertise available there.

[168] Potassium may rapidly rise to dangerous levels after extensive tissue injury and result in sudden unexpected death. These fatalities occur too early to manifest the histological features described by Bywaters in those who died days later from ARF.

Parsons goes on to say:

> "The introduction of the Bull dieting regimen…was a gigantic leap forward, enabling us to say goodbye to sodium sulphate infusions, decapsulating kidneys, old remedies, and fluid overload. Even with this dietary regimen, however, it was touch and go whether the uraemia or the returning renal function would win, and when severe trauma or infection was present lethal uraemia would develop by the sixth day. On witnessing such a case for the first time I felt dejected and disillusioned and retired to the library to read Dr Merrill and colleagues' experience with an artificial kidney. The answer was obvious. We had to get an artificial kidney. But what chance had an unknown man, a mere research fellow, of altering the entrenched opinion against dialysis in the United Kingdom? Luck soon came my way again." (p1558)

In this Parsons echoes other early workers in dialysis, who also later testified to the impact on them of individual patients whom they felt impotent to help.

This might be considered to be the key passage of Parsons' memoir, in which he seeks not only to establish himself as a visionary, identifying the solution to untreatable uraemia, but also to justify both his foresight and his determination to prevail against established opinion. Consequently, the passage merits further analysis, with the caveat that Parsons was writing at a distance of more than 40 years, towards the end of his life (he died of carcinoma of the prostate and was, in all probability, aware of this at the time of writing; it could therefore be considered that the BMJ article might have been a valetudinarian statement and justification of his life's work, for which Parsons felt that he had received inadequate recognition). The passage cannot be regarded as a strict record of events, but solely as a précis of his recollections of the circumstances in which he came to espouse dialysis. The first difficulty arises in trying to put a date to these events, if we accept for this purpose that this was a factual account. The "Bull regimen" was published in 1949 (Bull, Joekes et al. 1949) and Borst's similar treatment a little earlier (Borst 1948); Merrill's first papers on the use of the artificial kidney appeared in 1950 (Merrill, Smith et al. 1950; Merrill, Thorn et al. 1950). We must suppose that the events described by Parsons relate to the period 1951 – 1954 when he was a surgical research fellow, when as has been previously suggested, he was faced with managing acute renal failure patients not because of any previous special clinical expertise but because he had access to biochemical procedures superior to those offered by the hospital's routine biochemistry laboratory. Additionally, many patients would have had

urological causes of their uraemia. Parsons infers that he was familiar with the "old" treatments for uraemia and had found them wanting, as was the general realisation among those faced with managing such patients. Two further inferences can also be made: that he had access to a sophisticated dietetic service to make and administer Bull's recipe, and that before he had access to dialysis he was familiar with the general *medical* management of renal failure. Parsons published his experience of managing patients with renal failure due to a urological problem with the Bull regimen (Parsons 1954). (It is of interest that he modified the standard diet by adding aluminium hydroxide to sequester phosphate. In this he displays an early highly sophisticated understanding of the uraemic syndrome, anticipating by many years the recognition of the severe problems with hyperphosphataemia and its treatment). He had common ground with other early workers in the field, all of whom regarded dialysis as an adjunct to the medical treatment of ARF; the Leeds group's later espousal of the total management of these complicated patients was a major contribution and will be discussed later. Thus it may be presumed that, in the early 1950s, Parsons had at least some experience in the treatment of ARF. It is not possible to discover how widely the "old" treatments had been used at the Infirmary. If decapsulation of the kidneys had been employed, then this would properly have been the province of the urology department.

If Parsons' account is, for the moment, accepted at face value, a more fundamental question arises. If he was managing patients with ARF, why did he have to "retire to the library" following the traumatic experience of "failing" a patient. Two possible explanations present themselves, both speculative but both perhaps giving some insight into the status of dialysis in the early 1950s and/or the position of those attending uraemic patients, well before the concept of "nephrologists" had appeared. Borst and Bull had both published in *The Lancet*, a high-profile British journal which would be expected to have been required reading, at least for Parsons' physician colleagues. Merrill, on the other hand, published his early papers in the *Journal of Clinical Investigation*: a prestigious American research journal[169] which might be supposed to have been unlikely to cross a surgeon's consciousness, but would have been familiar to a physiological investigator. It is not recorded whether Merrill had tried and failed to get published in a more high-profile general journal, but it is more likely that as dialysis was generally regarded as an experimental procedure the Boston group, who were academic

[169] The JCI was unusual in requiring authors to pay a fee for publication.

investigators, chose to publish in an academic journal. Whilst this may perhaps excuse a junior surgeon's lack of knowledge of available, albeit unproven, treatments it does raise the question of just how *au fait* was Parsons with the management of renal patients. Whereas Merrill's published experience may have been the most significant contribution to the dialysis literature thus far, it had been preceded by a number of reports in both British and American surgical and medical journals of the use of haemodialysis, peritoneal dialysis, and other interventions such as intestinal lavage.

It is also questionable just how "obvious" the need for an artificial kidney was at that time. Merrill's 1950 papers report 40 analysable patients who each received one or, at most, two dialysis sessions. Of these 40, 18 had chronic renal failure and 14 (78%) died shortly after dialysis. 13 (60%) of the 22 patients with ARF survived, an outcome not dissimilar to that reported by Bull, who reported a 64% survival with his conservative regime. It is difficult to assess just how ill Bull's patients were, but the 4 who died seem to have been comparable in severity to the majority of Merrill's cases, in whom dialysis appears to have been a treatment of last resort following failure of a conservative regime similar to Bull's. It is possible that Parsons made a sophisticated comparison of the various published series, and came to the conclusion that most if not all of Merrill's dialysed patients had such advanced uraemia that they would have been expected to die without some sort of further intervention. However, the clinical and laboratory details in the published reports of the period are limited and do not allow conclusive comparison between series or whether they do actually report like-for-like clinical material. One might suggest that Merrill's 1953 paper (Swann and Merrill 1953) would have had a greater impact because of the wealth of clinical detail and careful argument. It was only later, as experience with the treatments accumulated, that it was appreciated that the conservative dietary regimens were suitable only for non-catabolic, milder cases. Nevertheless, whatever the particulars of Merrill's cases and notwithstanding the fact that each received what would now be considered a very inadequate amount of dialysis, it is difficult to see how Merrill made, at that time, an "obvious" case for dialysis. Unless, that is, the reader's frame of mind meant that he wanted to utilise an intervention, any treatment, that might make him feel that he was able to do everything for his charges. Parsons' account of a damascene moment, the realisation of the necessity for an artificial kidney, is also rather shakily supported by the available evidence. Unless he did so at Parsons' prompting, and he gives no indication of this, it

was Pyrah who initiated contact with the Boston group and engineered the acquisition of an artificial kidney.

Pyrah had previously visited Boston and Chicago, where he had met Professor Charles Huggins, who later won the Nobel Prize for his work on the endocrine control of cancer. In Pyrah's own words (University Of Leeds Archive/Personalia/Pyrah/ 054/volume II), his early visits to the USA in 1952 and 1953 were more significant to the later introduction of dialysis to the UK than has been previously recognised:

> [My visit to Boston] "…showed me the value of the artificial kidney, of which there were none in Great Britain. A further visit…emphasized this when I went to the Massachusetts General Hospital [sic] to see Dr Merrill. It was evident that we must have an artificial kidney if we were to treat cases of anuria with any success. No money being available from the Ministry of Health, I persuaded Sir George Martin to allow the Board of Governors to allocate more than £2,000 from the free monies in the hands of the Board to purchase an artificial kidney."
>
> "Dr Parsons was entrusted with the working of the artificial kidney, to master the techniques and the snags, and to put it on a clinical footing."

In 1953, Pyrah invited Huggins to address the annual meeting of the British Association of Urological Surgeons, of which Pyrah was president, and arranged for him to receive an honorary degree from Leeds University. Huggins reciprocated these gestures by arranging a one year research fellowship in Chicago for Parsons. At the end of this time, Huggins facilitated a visit to the Peter Bent Brigham Hospital[170], Boston for three or four months to learn dialysis from John Merrill. (Parsons describes the PBBH as a "unique institution" and "the happiest hospital that I was privileged to join"). Among other cases,

[170] As previously noted, the Peter Bent Brigham Hospital held a pre-eminent position in clinical research, in line with its founders' ambitions (Vogel, M. J. (1980). The Invention of the Modern Hospital: Boston 1870 - 1930. Chicago, University of Chicago Press.). The history of the PBBH is perhaps unique. Brigham a merchant with railroad interests, died in 1877 leaving his fortune (worth $4.2 million in 1902) to establish a hospital in Boston. In the 36 years between the endowment and the actual opening, "the entire project had undergone drastic change", largely because Harvard University established a medical school on the same site. "Brigham had been underwritten as a hospital in the traditional, nineteenth-century sense of the term, a charity and refuge for the sick poor of Suffolk County. It opened committed to the best in medical science, perceiving its role as that of a laboratory for the advancement of medicine. The narrow geographic limitations determining eligibility for admission were swept aside…its relations with the medical community were different…Brigham did not make its appointments from a local, inbred medical faculty which perceived its service in part in terms of a narrow stewardship. Rather, it turned over its appointments to a medical school seeking a national reputation." (Vogel 1980, pp 86-87). Even in the 1920s, potential donors were reassured that their gifts would not be used for the care of the poor, but rather for research and construction. This deliberate striving for pre-eminence, and its wealth, attracted the most distinguished practitioners, so that the first chiefs of the major services were Harvey Cushing, Henry A Christian, and William T Councilman. Later, the nascent specialty of clinical nephrology flourished within this established (and funded) research milieu.

Parsons helped with the dialysis of the recipient of the world's first twin-to-twin transplant. According to Parsons (Parsons 1989):

> "At the end of 1954 there was little enthusiasm in Leeds for an artificial kidney, nor any space to house it. Nevertheless, I persuaded Professor Pyrah to write to the board of governors of the Infirmary asking for a Kolff-Brigham machine. Surprisingly, we got it and also a blank cheque to cover its operating costs for two years. At the same time Professor Pyrah successfully negotiated with the Medical Research Council for the formation of a research unit with him as director and me as assistant director and adequate research facilities and full financial support[171]. But my troubles were far from over as I still had to convince Sir Harold Himsworth, secretary to the council, and Dr Herrod [Principle Medical Officer] of the value of the artificial kidney – not an easy task as they had already been told that there was no place in British medicine for artificial kidneys. The interview lasted two hours, during which I described my experiences in Leeds and in Boston. This must have convinced them as Sir Harold dismissed me, saying, "Parsons, try it, but remember that the country is against you."
>
> The problem of housing the artificial kidney was solved by Professor R E [later Sir Ronald] Tunbridge [Professor of Medicine at Leeds], who agreed to put it in his new metabolic ward and appointed his lecturer in medicine, Dr Brian McCracken, to help operate it." (pp 1558-1559).

This anecdote of the reluctance of the MRC to endorse the development of dialysis in Britain has been widely quoted (Drukker 1989), and even embellished[172] and has been often used as an example of the resistance of the medical establishment to the use of novel technology in the treatment of kidney failure. It is assumed that the MRC received the negative advice from Dr Graham Bull of the Hammersmith Hospital and/or Professor Robert (later Sir, later Lord) Platt of Manchester who served as a member of the Council of the MRC from 1953 to 1957.

Parsons is not alone in seeking to portray himself as a visionary pioneer of medical technology, opposed by resistance from the Establishment. Alwall, Kolff and Merrill also propounded this theme in retrospective memoirs. There was undoubted reluctance to embrace the new technology, which amounted to more than mere indifference and was

[171] In fact, the Board of Governors of the Infirmary provided at least 25% of the salaries and running costs.
[172] It has been reported that this encounter with the MRC occurred whilst the machine was actually in mid-Atlantic in transit from Boston to Leeds.

1923	BSc (Hons), Physiology, Leeds University
1924	MSc (Hons), Physiology, Leeds University MB ChB (Hons), Leeds
1930	Surgical Tutor, Leeds University
1936	Consultant General Surgeon, LGI and St James's Hospital, Leeds
1950	Established Department of Urological Surgery
1956	Personal Chair of Urological Surgery, Leeds University Honorary Director, MRC Metabolic Disturbances in Surgery Unit

Figure 5.2. Lesley Norman Pyrah (1899 – 1995)

indeed active resistance based largely on a lack of conviction of the utility of the technology. However, it is hard to discover any collateral evidence that the MRC or the LGI were anything other than supportive of the Leeds enterprise; the support may initially have been non-committal as to the value of dialysis but was substantial in terms of finance, personnel and facilities. The MRC records in the National Archives contain no mention of the artificial kidney until after it was established and then the record is simply of annual reports from Parsons, as assistant director of the MRC unit, of the activities and research associated with the device. The MRC continued, and indeed increased, the funding of the Leeds unit for many years, including its perpetuation after Pyrah's retirement when the unit morphed into the MRC Mineral Metabolism Unit at the LGI, under the direction of Professor BEC Nordin. Although Parsons and the dialysis programme had by that time long ceased to be a charge on the MRC, the renal unit and

the MRC unit shared clinical and research facilities which were, at least in part, underwritten by the MRC. David Hamilton (1984, p93) has also been unable to discover any formal referee's report, or any other mention of the contemporary attitude to the use of the artificial kidney within the extant MRC records. In Hamilton's words "such phrases tend to become embedded in the history of the times, and it was worth exploring the matter further." Consequently, Hamilton interviewed Sir Harold Himsworth, who had no recollection of the event.

5.5 Negotiating the start of dialysis

5.5a. Medical Research Council

The Pyrah collection in the Leeds University Archives contains extensive correspondence with the MRC regarding the establishment of the Metabolic Disturbances in Surgery Unit, and includes remarkably little on the artificial kidney. According to Pyrah's notes, his first submission to the MRC was ignored, so he invoked the help of Sir Cecil Wakeley, President of the Royal College of Surgeons. Following Wakeley's representations, Sir Harold Himsworth (Secretary of the MRC) entertained Pyrah to lunch at the Athenaeum "and financial assistance gradually came forth". In the formal submission to the MRC (20 December 1955), Pyrah wrote:

> "The personal support of the Chairman of the Board of Governors has already been given for the purchase of an artificial kidney and it is hoped that we shall have one within the department and space and staff to use it, as soon as permits can be obtained and the apparatus purchased from the United States of America. Dr Parsons is to take a leading part in the development of this ancillary aid for the treatment of cases of renal failure."

There is no further mention of dialysis until September 1957 in the extensive correspondence between the MRC and Pyrah (although Parsons had by then submitted at least one report on its use).

What is clear is that Pyrah, over a number of years, worked assiduously to support and promote Parsons, and to ensure that he was given a permanent position. In a letter of 14 February 1955 to Himsworth, Pyrah endorses Parsons and goes on to say "Dr Parsons has decided that he wished to make research work his life's career and in my opinion he has the necessary qualities, energy and ambition to achieve this." The MRC, however, appear rather cautious in this matter, despite pre-emptive local action by Pyrah, through the machinery of the Infirmary. Thus, in a letter of 9 November 1955, Mr Arnold Tunstall (Secretary to the Board of Governors) reported that the Board were unanimous

in agreeing that Parsons should be awarded the rank of consultant (research) for the duration of his appointment as Deputy Director of the MRC Unit. The MRC, however, were not happy with this as the title 'deputy' implied that Parsons would succeed Pyrah as Director (indeed, this had been Pyrah's stated intention as he had proposed that he should be *honorary director* for a period of five years, with a seamless succession to Parsons).

The key letter from the MRC, dated 30 January 1956 not only confirms approval of the Unit and the suitable funding, together with agreement with the Board of Governors that they should contribute 25% of the costs for five years, but also discusses at length the position of Parsons. The MRC insisted that Parsons should have the title of *Assistant* Director, without assurance that he would succeed to the directorship. "This consideration does of course have a bearing on the appropriate starting salary…", the MRC proposing that Parsons should receive £1970 per annum, the top point of the MRC Senior A scale, which was below that of medically-qualified consultants. "This again has a bearing on the question of his status as a clinical research worker *vis a vis* the Board of Governors. As you will recall, the Clinical Research Board were a little puzzled by the suggestion that he should receive an honorary "research" consultant appointment, since there is no such category of clinical appointment in the National Health Service. It is realised, of course, that Dr Parsons is in a rather special position, in so far as his qualifications would not entitle him to an honorary appointment as Consultant in Surgery, and we wondered therefore whether there might be a possibility of his being considered for an honorary appointment at the appropriate level in the field of Medicine, defined in terms of his special experience in the metabolic disturbances associated with surgical conditions….[I]t is suggested that in all the circumstances the grading of S.H.M.O. would be most fitting at this stage".

The official letter to Sir George Martin (Chairman of the Board of Governors) dated 20 July 1956 does not mention Parsons, but confirms the financial arrangements establishing the MRC Unit at the Infirmary, to which the Board would contribute £2500 per annum for five years, together with the clinical facilities and clerical support required by Pyrah. Pyrah eventually conceded the grading of Parsons, and in a letter of 2 March 1956, asked if the MRC would accept some sort of local arrangement for his clinical title.

There was no further correspondence on this particular issue, but Parsons was not promoted until 1961, and then with a possibly unique title of Consultant in Clinical

Renal Medicine, perhaps indicating that he was neither physician nor surgeon. But even this appointment was not without controversy. It had become clear that if the consultant post were to be advertised for renal medicine, Parsons would possibly face competition from physicians with an interest in nephrology who would be willing to take over the management of the dialysis service, which Pyrah wanted to retain as a self-contained activity within the remit of the Urology department and its associated research structure. Thus we find Pyrah writing to the MRC on 23 November 1960 attempting to construct the post, with MRC links and support, to allow a non-competitive transition to consultant status. The MRC response indicates that they considered the proposal to be irregular, suggesting that the proposed arrangement (some sessions to be funded by the MRC) as most unusual, if not completely without precedent. In the event, it appears the Infirmary made an internal appointment or promotion, which probably explains why Parsons' job carried the unusual title.

The unusual circumstances of Parsons' appointment as a consultant are evidence of the then autonomy of the teaching hospitals. He was appointed without advertisement or competition to a uniquely structured and titled post, thereby overcoming the lack of conventional higher qualifications from one of the Royal Colleges. The promotion was a *de facto* recognition by the LGI of the activities he was already performing. The informality of the arrangement had unforeseeable long-term repercussions. Parsons was ill-prepared for the way in which the specialty of nephrology unfolded to encompass not only renal replacement therapy but also the medical management of the whole spectrum of kidney disorders. It may well have been that his career progression set him apart from his physician colleagues, leaving him somewhat professionally isolated.

The artificial kidney next appears in the Pyrah/MRC correspondence in September 1957, when Pyrah attempts to enlist the help of the MRC to rescue his plans for a clinical base for dialysis. The Infirmary was constructing a 6-floor mixed ward and laboratory block (the Martin Wing), the original plans of which had included a ward for the renal patients and dialysis. Following a report from the University Grants Committee which had been highly critical of the facilities for research and teaching available to the academic departments of surgery and medicine, the UGC and Leeds University (both of whom were in part funding the project) secured priority for the building and ensured that the plans were modified to expand the academic resources, but at the expense of Pyrah's department. In the meantime, Pyrah had secured a promise of £60,000 from the Wellcome Trust in 1956 as about half the cost of a new wing to house research

departments, including the MRC unit and the academic department of medical physics with which it was closely allied. The Wellcome Trustees flatly rejected a proposal for additional monies to construct an extra floor on this block to accommodate the clinical dialysis service (the Wellcome Trust on principle not funding what they considered to be NHS clinical services).

Pyrah's letter of 18 September 1957 is a remarkable document. He summarises the workload and results of the artificial kidney and attempts to apply some psychological pressure: "Moreover, many of these patients developed anuria after maternity or after abortion, patients for whom the Ministry of Health has always expressed special concerns." He goes on to detail the problems experienced with hospital acquired antibiotic-resistant infections, reporting that six or seven patients had died from nosocomial Staphylococcal enteritis and of these, four were in the recovery phase of their episode of acute renal failure. He details the investigations into the problem and concludes with a statement that rings true half a century later: "These resistant organisms seem to be everywhere, including blankets, bed clothes, and nurses' throats." He suggests that the solution to the problem is to provide special, clean treatment rooms for the exclusive use of the artificial kidney, which were to have been provided in the Martin Wing but could now be provided if an additional, clinical, floor were to be added to the Wellcome Wing. He requested that the Clinical Research Board should send a recommendation to the Ministry of Health (and thence to the Board of Governors of the Infirmary) for the provision of a research ward primarily for the use of the artificial kidney.

The response, dated 8 October 1957, from Dr FJC Herrold of the MRC appears to be an understatement of the MRC's longstanding concerns about dialysis: "…we are, of course, aware that you had included work with the artificial kidney in the programme of the Research Unit's activities. What we are not quite clear about is the scope of the research aspect of this project…" This produced a sharp, but strangely delayed response from Pyrah, dated 24 March 1958 (one might speculate that the response had been delayed to allow the Unit's first publications to appear in print):

> "…and the two papers published in the British Journal of Urology [(Parsons and McCracken 1957; Parsons and MacCracken 1958)] in December, 1957, which allowed a comparison of the results achieved in the unit at Leeds with that at the Post-Graduate Hospital, showed, I think, the much more effective use to which our apparatus has been put and the greater degree of clinical success."

However, Pyrah, having scored points against the rival hospital which was always assumed to have had a closer relationship with the MRC, then defeats his case by admitting that dialysis was foremost a clinical activity:

"There has been a great deal of spade work to be done and it is only now that the apparatus is moving from the sphere of clinical research to routine work."

The exchange did produce some rather grudging support from the MRC, in a letter of 4 June 1958 to the Board of Governors:

"…contrary to expectations when the Unit was set up in October 1956, the Unit has not yet obtained adequate facilities of the special kind needed for metabolic work or for work with the artificial kidney."

This ignores the fact that during the negotiations for the MRC Unit at the Infirmary, no mention was made of providing facilities specifically for dialysis (possibly because it was not known what might be required, or possibly because it was considered a relative minor part of the whole enterprise with an uncertain future). In any event, an additional three floors were eventually added to the Wellcome Wing in the early 1960s, funded from a variety of official, local and charity sources.

5.5b. Leeds General Infirmary

Available evidence suggests that rather than showing "little enthusiasm", the authorities, both clinical and managerial, at Leeds were remarkably supportive[173], providing clinical facilities, staff, and very significant financial outlay. Whilst it was the practice of the time that relatively little was committed to paper record, particularly in the form of background documentation, the minutes of the Board of Governors and of the various Infirmary medical committees paint a picture of carefully considered endorsement and support. Parsons was right to suggest that space for the dialysis machine was at a premium and had to compete with other clinical demands, as the extracts from minutes cited below clearly demonstrate.

Finance and General Purposes Committee, minute FGP2821, 16 January 1956[174].

Under the heading "Department of Urology – Purchase of Artificial Kidney:

[173] The support provided by the Governors is in keeping with some patterns of decision-making in relation to innovation. Scott, W. R. (1990). "Innovation in medical care organizations: a synthetic review." Med Care Res Rev **47**: 165-192. in which "older and more parochial officials were less likely to innovate, but when they did, surprisingly, they were more likely to introduce changes entailing greater discontinuities." (p169) (This is based on: Becker MH. 1970 Sociometric location and innovativeness: reformulation and extension of the diffusion model. Amer Sociol Rev 35: 276-282).

[174] Copy documents available in the University of Leeds Archive (Personalia/Parsons)

"An application was received from Mr L N Pyrah, Consultant Surgeon to the Department of Urology for the purchase of an artificial kidney…, and for the services of two senior biochemical technicians for work in the research section of this department…After careful consideration it was agreed that all the proposals be approved as follows and the cost borne from the Endowment Fund for a period of three years in the first place and then be subject to review as to whether all or any part of the cost could be considered as normal National Health Service expenditure:-

(a) Artificial Kidney (5,500-6,000 dollars) - £2,500 including transport etc.

(b) A Senior Laboratory Technician - £550-£650 per annum

(c) A Laboratory Technician - £450-£500 per annum

It was agreed that it be made clear to Mr Pyrah that approval given to the employment of the two technicians was on the understanding that they would assist with other urological research work whenever they were not directly involved with duties arising from the use of the Artificial Kidney…"

In purely financial terms, this huge commitment by the Board of Governors (the MRC records also show that the Infirmary also provided 50% of Dr Parsons' salary) was made possible by the wealth of the Infirmary. As will be indicated below, the indirect financial support was actually greater than this. The Infirmary clinical and managerial authorities obviously went to some considerable lengths to facilitate space to accommodate the dialysis machine:

Board of Governors: Infirmary House Committee Minute 2413, 10th September 1956:

"It was reported that the artificial kidney approved by the Board…had now arrived from America and the question had arisen as to where it was to be housed.

The original intention of Mr Pyrah was to use a 2-bedded room on ward 24 but, more recently, the view had been expressed that it might be better if it were directly connected with the new Metabolic Ward, possibly by construction of an annexe to the ward for the purpose. In the meantime, however, Mr Pyrah and Dr Parsons had asked if the artificial kidney could be fitted up in one of the 2-bedded rooms in the Metabolic Ward and to this suggestion Dr Towers, as Chairman of the Faculty, had given qualified approval subject to discussion at the next meeting of Faculty. It was explained that the use of this apparatus in connection with the Metabolic Ward was expected to assist in the recruitment and retention of the specially trained nursing staff essential to that ward. It was agreed that, subject to the approval of the Faculty, the temporary housing of the artificial kidney in a 2-bedded room of the

Metabolic Ward be approved, together with minor alterations for water supply, drainage, etc."

Board of Governors Minute2551, 1st October 1956:

Report of Infirmary House Committee: Artificial Kidney:

"Referring to Minute 2413, Dr Garland stated that he thought that the Board would like to know that the artificial kidney had been used for the first time on Sunday, September 30th".

Board of Governors Minute 2558, 1st October 1956:

Recommendation from Faculty:

"(a). Artificial Kidney. That this apparatus be housed in one of the 2-bed rooms in the Metabolic Ward as a temporary measure but that it later be transferred to the Martin Wing if the plans mature. This was agreed."

The significance of the agreement to accommodate the dialysis machine in the Metabolic Ward (and also some of the renal patients, the others being housed in the beds of the Professor of Medicine, Sir Ronald Tunbridge) is that it required other clinicians to relinquish access to parts of the new facility. Control of and access to beds is a perennially contentious issue among clinicians. Incorporation of the dialysis machine into the medical (as opposed to surgical) facilities not only provided junior medical staff, as acknowledged by Parsons, but also unwittingly eased the transition of dialysis from a surgical to a medical activity.

The Infirmary clearly took great pride in its achievement of establishing dialysis, as evidenced by the somewhat inaccurate entry in the hospital report for 1956/7 (p23):

"Sir Harold Himsworth KCB, MB, FRCP, QHP, Secretary to the Medical Research Council officially opened the new Metabolic Ward on 1st October 1956. As from 1st October 1956, a major development at the Infirmary was the setting up by the Medical Research Council, for an initial period of five years, of a Research Unit on Metabolic Disturbances in Surgery. The Unit is under the direction of Professor LN Pyrah and Dr FM Parsons has been appointed Assistant Director. It is the only research unit of its kind in this country, the one other comparable centre being in the United States. In addition to providing the artificial kidney, extensively used in this work, the Board agreed to meet from endowment monies 25% of the cost involved."

The report of official opening of the ward is accompanied by a photograph taken by the Yorkshire Post showing Parsons, Himsworth and Sir Donald Kaberry (Chairman of the

Governors) discussing the dialysis machine. The available evidence is that the MRC and the Infirmary, marshalled by Pyrah, closely cooperated in providing, and generously funding and staffing, the dialysis machine and the facilities for its use.

5.5c. The Ministry of Health

It is clear that the Ministry of Health (MoH), through Dr (later Sir) George E Godber[175], not only took a close interest in but was also supportive of the establishment of dialysis at Leeds. At that time, the London and provincial Teaching Hospitals remained outside the Regional and Area Health Boards, being directly funded and supervised from Whitehall. It is therefore understandable that there was direct communication between Godber and, for example, Pyrah. Thus the Infirmary Metabolic Ward Committee noted on 15 December 1956 [less than three months after the first dialysis] that:

"Dr Godber is at present circulating the Regional Hospital Boards of Northern England to tell them we are willing to accept suitable patients for treatment."

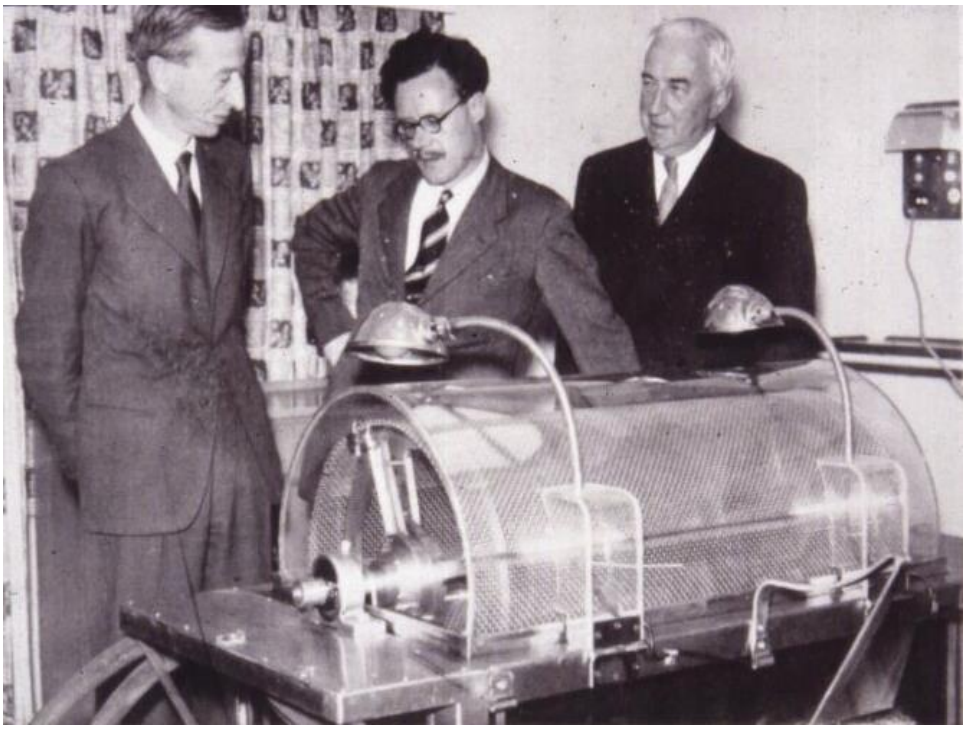

Figure 5.3. Demonstration of Kolff-Brigham dialysis machine at Leeds, October 1956. Sir Harold Himsworth (L), Dr Frank Parsons, Sir Donald Kaberry, Chairman of Governors, LGI (R).

[175] George Godber (4.08.1908 – 7.02.2009) was at that time Deputy CMO before becoming "one of the country's greatest Chief Medical Officers" (Sheard, S. and L. J. Donaldson (2006). The Nation's Doctor: The Role of the Chief Medical Officer 1885 - 1998. Abingdon, Radcliffe.)

The MoH was also keen to accept some of the kudos accruing from the developments in Leeds. The November 1956 edition of the journal *Hospital and Health Management*, published by Her Majesty's Stationery Office on behalf of the MoH devotes two pages to a piece entitled "Leeds General Infirmary (United Leeds Hospitals): New and well-equipped metabolic ward opened." Although the article does not mention the dialysis machine (it is based on the opening of the Metabolic Ward on 1st October 1956, which occurred only hours after the first dialysis), it goes into considerable laudatory detail on the facilities[176]. Significantly the anonymous article notes that, for the six beds of the ward, "a large nursing staff varying from five to nine is required and these are being provided by the Infirmary."

In a long, detailed and in places personal letter to Dr Godber, dated 17th August 1957, Pyrah suggested that the demand for dialysis and the interest that the procedure evoked exceeded their expectations. He also makes some prescient comments on the demands placed upon staff and for the need for planning of expanded dialysis services:

> "You will remember that some eighteen months ago I applied to you for permission to purchase an artificial kidney from Boston, USA for my department, the money amounting to two or three thousand being provided by the Board of Governors of the Teaching Hospital…We did not quite foresee the demand that there would be for the use of this machine…It has been found that a team of people has got to be available at any time for the treatment of these cases when they reach hospital. Cases have been sent in from Scotland, the Newcastle area, the West of England and as far south as Birmingham. The only other artificial kidney in the country is at the Post-Graduate Hospital which presumably attracts patients from the London area.
>
> This rather spectacular venture has been in the beginning more successful than we hoped, in rescuing a number of patients from complete anuria. You will see from the relative success that the kidney has achieved, and also the interest that it has

[176] Hospital and Health Management, November 1956, pp 316 – 317: "…a portable examination lamp…produced by Best and Lloyd of Birmingham in collaboration with Infirmary doctors. The adjustable head contains two 40-watt fluorescent tubes with removable Perspex panel and the column is fitted with instant start gear and a handle for easy movement." (p317)
"Other interesting features of the new single-storey ward are ceiling panel heating of the Frenger type, air-conditioning of all accommodation other than sluices, etc, double glazing of windows, two research laboratories, and an attractively decorated and furnished day room. A consultation room is also included in the suite which has cost £31,500 in all."
"Accurately controlled refrigeration is an important feature of the laboratory facilities…specially designed Prestcold cabinet to take a wall partition across the centre" [to allow transfer of specimens without direct contact between ward and laboratory].

> caused up and down the country, that it is clear that the number of cases requiring its use is more than we supposed. We have had an enquiry from Edinburgh about the cost, staffing etc. of an artificial kidney and I believe that it is the intention of the Glasgow hospital to purchase one, too. It may be that another one could be established in the Midlands possibly Birmingham. These points are becoming of practical importance to us, because our existing team has already on some occasions been overworked with these arduous and difficult cases. It may be…that the ministry would like to hear our views upon this problem as to the setting up of artificial kidneys in a small number of centres elsewhere in the country."

Pyrah then goes on to raise the problem of "antibiotic resistant" nosocomial infections in the Metabolic Ward and the need for a dedicated, clean area for the dialysis machine. There was further correspondence through 1957, largely with Miss Dennis, Deputy Medical Officer about technicalities of dialysis, its use in poisonings, costs and staff provisions.

5.6 Conclusions

From the available documentary evidence, and notwithstanding the partial account given by Parsons, it would appear that the establishment of a dialysis machine in Leeds resulted from the persistence of Parsons, who recognised a clinical need that he was equipped to address, significantly supported by his mentor Pyrah. Pyrah would appear to have been the more significant player in facilitating the establishment of dialysis and negotiating the research-orientated facility that enabled its introduction. Their representations, both local and national, resulted in considerable enabling support from the hospital, its clinicians, and from the MRC. The start of dialysis in Leeds in 1956 was certainly a landmark in the development and deployment of medical technology in Britain, but it is not possible to sustain the notion of an individual pioneering against general adversity.

6. LEEDS AFTER 1956

6.1 Introduction

For the unit at the LGI, the late 1950s was a time of consolidation: establishing relationships with funding authorities, the wider medical profession and the public; feeling their way toward what they came to regard as the 'best' practice in dialysis; meeting and circumventing unforeseen problems; consolidating personal standing. The early 1960s marked a period of radical change in the practice of renal medicine with the advent of the technical capability of providing long-term dialysis for those with chronic, irreversible renal failure. This important transition period has received attention in the literature (Drukker 1989; Peitzman 1997; Stanton 1999; Peitzman 2001; Cameron 2002; Peitzman 2007; Crowther, Reynolds et al. 2009) but here will be referred to only as it impinges on the main theme of ARF and its treatment in the UK and, particularly, Leeds.

1958 appears to have been the year when those involved in the Leeds artificial kidney took stock of the situation. That this review occurred within two years of the first dialysis reflects the interlinked interests and pressures of the various parties (which included the MRC, Ministry of Health, University, Board of Governors, and the staff of the LGI). This, as it were, 'internal' review was complemented by 'external' assessments made by visiting clinicians, indicating the increasing interest in dialysis in the UK and the then status of Leeds as the centre whose success had rapidly made dialysis a clinically acceptable procedure.

6.2 Communication with the Authorities

Within the LGI, the factors precipitating assessment of the situation included pressure on staff, facilities and accommodation from the unpredicted demand for dialysis; Pyrah's ambition to expand his department and, particularly, to protect the research element of his endeavours; and continuing uncertainty over Parsons' position and prospects. The significance of this episode lies in part in the internal and external machinations influencing the expansion of a specialist department, and also in the review of activities which formed the necessary basis of the protagonists' arguments. The crux of the problem was the desire to add another (fourth) storey to the research wing planned for the LGI for which Pyrah had personally negotiated funding from the Wellcome Trust. This money had been granted in January 1956, although not announced until much later. Indeed it appears from the correspondence that Pyrah did not inform the MRC until 1958. In the interim, Pyrah had successfully sought further private and charitable

donations but had been less successful in his dealings with the University and the hospital. He had hoped, and perhaps even assumed, that he would be given a sizeable allocation of beds (for both clinical use and metabolic research) in the new ("Martin") wing of the Infirmary jointly funded by the University and the Governors. Pyrah's aspirations were confounded by the combined power of neurosurgery (a regional centre headed by a surgeon who had achieved national status during the war) and the University, which was under pressure from the funding authorities to improve the facilities for the academic departments. At the same time, it became clear that the cost of the Wellcome Wing would be at least 25% greater than both the estimates and the available monies[177]. This shortfall (some £35,000) meant that Pyrah was unable to look to the Governors or the University, both of whom were already (over-) committed, for funding of the desired additional floor to house both the artificial kidney and its patients, and the clinical metabolic studies.

His political and financial problems were compounded by intense unforeseen clinical pressures. The renal unit had been remarkably successful in recruiting patients as a result of both their own activities and support from George Godber at the MoH. They had however run into an apparently intractable problem with severe, often fatal, hospital-acquired infections with antibiotic-resistant organisms. The solution to this was seen to be the provision of single-room accommodation for the renal patients. Neither this nor the necessary beds to accommodate the demand could be provide by the rather *ad hoc* arrangements in the Metabolic Ward, where Parsons was already occupying on average twice the concessionary allocation of beds. Unsurprisingly, there is a distinct note of desperation throughout Pyrah's correspondence with the MRC and MoH. In April 1958 a lengthy submission to the Clinical Research Board requested support from the MRC in an approach to the MoH for additional capital funding. Pyrah's letter included an appendix by Parsons detailing the patients treated with the artificial kidney together with on-going and proposed related research[178].

[177] Wellcome gave £60,000 on the strict understanding that the facility would be exclusively for research, and which was to be matched by other donations to provide clinical facilities. According to Pyrah (letter to Dr FJC Herrold, MRC dated 7.10.58) the architect significantly underestimated the costs which were not revealed until the sealed tenders were opened.

[178] The report (National Archives FD1/8833) of patients treated to April 1958 supports Pyrah's claim that Leeds was markedly more successful than the other unit (at the Hammersmith) then functioning, but also shows that they were still feeling their way in diagnosing and selecting patients suitable for short-term dialysis.

DIAGNOSIS	NUMBER	SURVIVAL
Chronic nephritis	6	0
Subacute glomerulonephritis	3	2
"Dialysed for diagnostic purposes, and then irrecoverable renal lesion found"		
Diabetic coma	1	1
"Pre- or post-renal lesions"	7	6
Acute Renal Failure - Obstetric - "early months"	5	5
- "late months"	8	8
- Major operations	10	2
- Accidental trauma	2	1
- Hepato-renal syndrome	4	1
- Miscellaneous	4	3

Table 6.1 Report to MRC of Patients Treated to April 1958

In the report, Parsons notes that 57 patients had received a total of 85 dialyses and that only two ARF patients were referred from Leeds and highlights the success of the obstetric patients. However, the report does not exactly tally with the contemporaneous records in the renal unit notebooks: at least 70 patients had by then been dialysed at least once, of whom a third were referred from Leeds hospitals.

Both the MRC and Godber at the Ministry were supportive of appeals to other parties, but appear not to have directly contributed to the additional capital costs. The MRC repeatedly expressed private reservations that the work of the Leeds unit was primarily clinical without a solid research basis, and their enthusiasm must have been further dampened by a less than flattering report of a visit by a senior member of staff (Dr RC Norton, later PMO of the MRC) to Leeds in September 1958 (my italics):

> p2. "Prof. Pyrah himself holds the key position for the unit's existence and functioning…He is clearly a central figure in hospital/University politics and has great influence over the present Chairman of the Board…Apart from this, however, Prof. Pyrah did not strike me as having much to contribute on the purely research side…*he did not give the impression of having a clear research strategy*…I think it probable that we may get a proposal from him…before long…*I think it should be examined with the greatest caution.*"

"My view is that the unit consisted of too few people trying to do far too much…and I wondered whether they were going to be able to cope. Certainly there is a danger of their efforts becoming too diffuse."

p3. "I was however in some doubt whether even he [Parsons] was certain in his mind about where he wanted to go next. He had a lot of ideas and the spark and energy which with luck might enable him to go a good deal further. I felt, though, that he would soon need to have a frank talk…to get some scientific guidance of a sort which he is not getting from Prof. Pyrah."

"The group's relationship with the hospital seemed very good, and there was close integration. Dr Parsons and his artificial kidney had become quite a hospital institution, and he was evidently widely accepted on this informal basis…How far he will go on being so, should there be changes in the present consultant staff, and particularly if and when Prof. Pyrah goes, remains to be seen…*Dr Parsons holds no official qualification which would qualify him for a consultant post* on the hospital staff."

"The group's relationship with the University also seemed on the whole satisfactory…On the financial level relationships with the University did not appear quite so cordial…"

"The group's accommodation seemed barely adequate and very muddly… There was no room for any paperwork to be done, and Dr Parsons…had tables in draughty corridors where [he] endeavoured to write up results and do some reading. I got the impression however that the hospital had really been fairly generous over accommodation, considering its own limited facilities."

Through 1959 and 1960, the MRC spent a lot of time considering the future of Pyrah's unit, the funding for which was due to expire on 31.12.60 (National Archives FD1/8835 and FD1/8836). After much discussion, and several visits to Leeds, it was decided to support the unit until Pyrah's retirement in 1964, and thereafter to support a unit for research in mineral metabolism (bone disease, renal stones, etc). A potential future director was identified in 1960: Dr BEC Nordin, a physician-scientist at Glasgow. The selection was made in conjunction with Leeds University, which had attracted Professor Forman, who had similar interests, to the Chair of Pathology.

Throughout this period concerns were repeatedly raised within the MRC about the role and future of Parsons. It was clear that dialysis and Parsons' role therein could no longer be considered to be research but had become entirely a clinical service. There

ensued complex tripartite negotiations between the LGI, the MoH and the MRC. The bargaining between the various parties appears to have been largely personal and verbal, only the conclusions being committed to paper (together with some rather tetchy notes and correspondence on minor matters such as the salaries of the laboratory bottle washers). It is clear that Pyrah was the key negotiator and one suspects that Godber was instrumental in achieving the final outcome, which was unusual if not unique but nevertheless extremely satisfactory to all concerned. The MRC took on the entirety of the funding of the research element, thereby relieving the Board of Governors from their contribution. The NHS (referred to throughout the correspondence as "the Exchequer", reflecting the then special funding arrangements for teaching hospitals) absorbed the whole costs of the dialysis service, including additional medical and other staff. The hospital provided the beds and support facilities, both for renal patients and for metabolic research. The MoH approved and funded a post entitled "Consultant in Renal Physiology" for which Parsons was the only candidate considered. This neat compromise avoided the problem of his lack of higher medical or surgical qualifications. Overall, this settlement illustrates the administrative arrangements in what in many ways was a transitional period between the inception of the NHS (with the negotiated integration of the previously self-governing and vehemently independent voluntary teaching hospitals) and the managerial reforms commencing in 1974: the special status and direct funding of the teaching hospitals, with their well-established pathways to the top of government; the power, influence and financial clout of Boards of Governors; the influence of senior doctors; and the freedom to approve and fund a "special case". In any event, Parsons was established and able to practice dialysis together with some research, variously funded by charity, the Governors and the University. The Wellcome Wing became six floors, of which two were clinical. Parsons and Pyrah turned their attention and energies to a new form of treatment: transplantation.

6.3 Communication within the profession

There were aspects of communication by the Leeds unit other than 'official' ones which arguably had a greater effect on the establishment of dialysis in the UK. These included advocacy of their way of doing dialysis within the profession, both informally and by publications, and wider publicity to the general public whose imagination (and charitable support) was gripped by the 'new' technology of dialysis. From the inception of dialysis at Leeds there was a steady stream of visitors, a number of whom stayed sufficiently long to participate in the dialysis procedure. Individuals who established

renal units in Glasgow, Newcastle, Middlesbrough, Cape Town, Sydney all served some sort of informal apprenticeship with Parsons. This reflects the sudden, and rapidly growing, professional interest in the treatment of renal failure as well as the pre-eminence in the field quickly established by Leeds.

A picture of the situation with British dialysis, and the prominence of the Leeds unit, is provided by a report dated August 1958 by Professors JS Robson and HAF Dudley, then senior registrars at Edinburgh Royal Infirmary[179]. From the perspective of the present work, this report gives a insight into the practicalities of dialysis at Leeds, details of which are lacking in the published papers. The date of the visit to Leeds is not given, but appears to have been in April 1958; the visits to the other two units (RAF Halton and the Hammersmith) probably a little later. As shown in Table 6.2, derived from information in the report, Leeds had by far the heaviest workload: approximately 7 patients/month, compared with 2.3/month at the Hammersmith and 2.2/month at the RAF. It is arguable that this greater experience, together with close cooperation with the academic department of medical physics, encouraged modification of the machine and dialysis technique, such developments not being reported from the other centres. To quote from the report:

> "Part of the good clinical results obtained by the Unit are attributed by them to the modifications carried out to increase the blood flow through the machine and its urea clearance. Flow through most artificial kidneys is about 350 ml./min. but by boosting the efficiency of the pump this has been increased to approximately 600 ml./min. The pump is modified from the original design by a fine "bleed" adjuster which varies the amount of suction applied. By this means and a slight increase in length of the cellophane tubing very high urea clearances have been obtained (300 ml./min.). By argument from analogy it is thought that the movement of other substances across the membrane is probably increased and that this may contribute to the good results In spite of these high rates of flow no haemo-dynamic difficulties have been encountered; this is probably attributable more to the excellence of the care of the patients and control of the machine than to any other factors."

[179] The full 11 page report, together with some related correspondence, can be found in the historical section of the ERI renal unit website (www.edren.org. Accessed 27.07.09). Uniquely among British centres, the ERI appears to have constructed a 'business case' for dialysis, for example by surveying potential need (ARF and poisoning), visiting other units in the UK to learn about machines and methods, and an assessment of costs for equipment, staff and supporting structures.

Centre	Number	Machine	Approx Cost	Operators
Leeds	121	Kolff-Brigham	£3000 £4-5 /dialysis	2 doctors 1 nurse 1 tech
RAF Halton	22	Kolff-Travenol twin coil	£750 £25/dialysis	2 doctors 2 nurses 1 tech
RPMS Hammersmith	40	Kolff-Brigham (Usifroid)	£2800 £4-5 /dialysis	2 doctors 1 nurse 2 techs

Table 6.2. Comparison of British Renal Units in 1958

As indicated by their footnote, the authors identified a problem with the practice of dialysis: the monitoring of the safe function of the machine. They develop this concern further in the comments about the visit to Leeds:

> "The machine is fitted with one flow meter of the ball type. Frequent re-adjustments of the pump seem necessary and are carried out according to the state of fullness of the last two cellophane coils of the kidney. This appears a crude method of estimating alterations in the volume of blood in the instrument and demands very careful watch by the responsible doctor. In our view this method of control is a drawback. If blood is not returned to the patient for any reason it is possible for him to be exsanguinated into the machine in a very short space of time."

The report implies that the observers identified this problem which was not apparent to the Leeds staff, but which had significant implications both at the time and, as would become gradually evident, for the future. Monitoring and control of the dialysis procedure would become driving forces in the development of the technology for two main reasons. As Robson and Dudley surmised, patient safety was potentially jeopardised by the absence of safety monitoring: they spotted the risk of exsanguination into the Leeds machine without continuous "very careful watch by the responsible doctors". The consequence of this potential threat to patients was the high level of staffing required to monitor these unsophisticated machines. Although not necessarily appreciated at the time, this was to become a major issue as the demand for dialysis

increased, at which point self-managing machines became essential. The report concludes with detailed recommendations for the machine (they opted for the Travenol-Kolff twin-coil on grounds of lower capital costs and greater ultrafiltration potential), staffing and support facilities for the establishment of dialysis in Edinburgh, the Artificial Kidney Unit there being formally opened on 20 May 1959.

The report was remarkably prescient in considering not only monitoring and control of the machines but also the control of infection and the establishment of fully self-contained renal 'units', issues which would receive increasing attention over the subsequent decade. The authors endorsed the then practice at Leeds and the Hammersmith that the management of renal failure should be under the control of both physicians and surgeons, although this would soon universally devolve to physicians and, eventually, to physicians within a defined specialty.

Parsons' espousal of the Kolff-Brigham rotating drum machine (to which he remained dedicated for many years) appears not to have entirely convinced others embarking on dialysis, including those who visited Leeds. The Hammersmith purchased the very similar Usifroid version of the Kolff drum in 1957 and Newcastle chose the Alwall machine. Others, including Edinburgh and the RAF[180] opted for the newly available Kolff-Travenol coil, which had many practical advantages. Unlike virtually every other unit worldwide, Leeds never used this machine.

Published papers have a variety of functions other than simply adding to the sum of medical knowledge. The early publications from Leeds (Parsons and McCracken 1957; Parsons and McCracken 1958; Parsons and McCracken 1958; Parsons 1959) were undoubtedly intended to be used to persuade the MRC to continue funding. Pyrah used them to support his contention that dialysis was a *research* activity, an argument further enhanced by the later more metabolic papers (McCracken and Parsons 1958; Blagg and Parsons 1960; Parsons, Hobson et al. 1961; Blagg, Parsons et al. 1962; Parsons 1962; Parsons 1963; Parsons and Fore 1963; Parsons 1964). Publications are also used to establish precedence and eminence for the authors and their institution. Leeds clearly regarded the Hammersmith as a rival, and again Pyrah argued to the funding authorities that his unit was the more successful (presumably meaning more patients and better outcomes). Strangely for an academic institution, the Hammersmith never published

[180] The RAF commenced dialysis in 1957 at the instigation of Air Vice-Marshall Aubrey Rumbal because, in March of that year, two pilots died of ARF following injuries sustained in an explosion. In fact, the RAF only ever treated civilians (approximately 8 per year, mainly pregnancy-related). (Professor JE Scott, pers comm., 5.08.2008).

their experience with dialysis and only once on ARF (Loughridge, Milne et al. 1960) after Bull left[181]. This contrasts with the significant output from Leeds which not only established the LGI as the centre for dialysis but also ensured that their system for the total management of ARF (Parsons, Hobson et al. 1961) became the standard for practice elsewhere.

The Leeds 'system' for managing ARF was based on close monitoring of patients' symptoms and clinical observations, and frequent biochemical measurements. They showed that by combining these facets, the likely course of the illness could be predicted with some certainty at an early stage. From this, and from experience, they were able to differentiate those who could be successfully managed with a conservative regimen from those who would likely perish without dialysis. Parsons also identified a third group: the critically ill in whom the situation was deteriorating at a rate at which delay in the institution of dialysis would result in an irrecoverable situation. These severely catabolic patients, usually with sepsis and/or extensive tissue damage, required early aggressive and frequent dialysis. Although Parsons' work flowed from the example of Merrill in Boston, his contribution was truly original: early dialytic intervention in the most challenging cases could not only be scientifically predicted but also, and more importantly, have a significantly positive impact on the eventual outcome. Parsons' observations and reasoning based on experience became assimilated into the practice of all subsequent nephrologists.

6.4 Communication with the public

The archive at Leeds University contains the scripts of numerous lectures given by Parsons to a variety of lay organisations predominantly, but not exclusively, in Yorkshire. The common feature of these organisations, such as Women's' Institutes and Rotary Clubs, is their strong culture of charitable giving. The event that fixed dialysis in the public's mind was the epochal first series of the BBC's Your Life in Their Hands (YLITH) screened in 1958. The subject for each programme was a 'new' 'cutting edge' treatment from a leading provincial hospital, to demonstrate that the best NHS treatment was available nationwide (Essex-Lopestri 2006).

[181] The sole paper (Shackman, R., M. D. Milne, et al. (1960). "Oliguric renal failure of surgical origin." Brit Med J **2**: 1473-1482.) lacks detail but reports that 277 patients had been "seen" in four years. Some information is given on 106 patients, of who 62 received dialysis with ~24% survival.

It is difficult to overstate the significance of the BBC's YLITH in the history of media coverage of medicine (Karpf 1988; Loughlin 2000; Loughlin 2002; Boon 2011)[182]. This was the first live broadcast of actual medical procedures and set the pattern for all future medical broadcasting. The series was meticulously planned in conjunction with various medical organisations, hospitals and government departments. The BBC arranged a meeting with a wide range of professional representatives to discuss the proposed series. Unlike other organisations, the *British Medical* Journal opted to send a non-medical member of staff as its representative. The presenter, Dr Charles Fletcher, a physician at the Hammersmith Hospital (the "television doctor"), selected major provincial hospitals to showcase modern medical practice. The programmes were carefully structured to allay professional concerns and, in particular, to avoid any adverse effect on the doctor-patient relationship. Thus: doctors appearing in the programmes were not named; reference to diseases was kept to the minimum necessary for an understanding of the treatments shown; descriptions of symptoms that might give rise to anxiety were avoided; the availability of other treatments or that treatments were not necessarily suitable for all was acknowledged.

Despite the preparations, the initial 1958 series received a hostile reception from the medical establishment, led by the BMA, who completely misjudged the public reaction. The audience averaged 8.25 million (Loughlin 2000), range 6.5 – 10.25 million (Karpf 1988), that is about a third of the adult population viewed the programmes at a time when television ownership was far from universal. Positive letters to the BBC outnumbered negative by 909 to 37 (Karpf 1988). The medical reaction to the novelty of the broadcasts, as voiced in the *BMJ*, included accusations of sensationalism, and the risk of audience squeamishness, encouraging hypochondria and pandering to morbid interest. Dr Essex-Lopestri, who had represented *The Lancet* at the meeting at the BBC, has contrasted the negative reaction of the *BMJ*[183] with the generous support of YLITH in the national press. Editorials in successive weeks in the *BMJ* opened with the title: "Disease education by the BBC" (Anon 1958; Anon 1958; Anon 1958; Anon 1958) in which YLITH was roundly condemned because "it will increase the number of neurotics in the population and stimulate, rather than lessen, fear of hospital treatment". Letters for and against appeared in the *BMJ* over the next 11 months. The national press took an

[182] It should be noted that Loughlin repeatedly incorrectly situates the broadcast of 8/4/1958 at Glasgow General Infirmary [sic] rather than correctly ascribing it to Leeds General Infirmary.

[183] *The Lancet* declined any editorial comment or review as it thought it had been journastically pre-empted by the vigorous debate in the BMJ.

entirely opposite view. The *Daily Mail* thought the "broadcast was a dignified and deeply interesting account". The *Manchester Guardian* agreed that "The experience…should have done much to show people that even the most feared diseases can be treated and cured". The *Manchester Guardian* later directly challenged the view expressed in the *BMJ*: "It is difficult to believe that anyone seeing this programme would not feel more hopeful rather than more frightened about the chances of survival…" It has been variously suggested that the initially negative response from the BMA was motivated either by a sense of exclusion (Karpf 1988) or by internal doubts over public relations (Loughlin 2000; Loughlin 2002; Loughlin 2005). Reports of the BMA Council meeting of 19.02.58 show that the main complaint was of a perceived lack of consultation during the preparation of the series, although some Council members thought that it was sensationalist by showing violence, horror and bloodshed[184].It would seem reasonable to suggest that the medical establishment felt threatened by this very public intrusion into their previously hermetically sealed world.

The strong emotions engendered by YLITH were reflected in a local Leeds spat between Tunbridge and Pyrah, between whom there appears to have been competition both for status and for ownership of the dialysis machine, and hence the derived kudos. A letter dated 3.03.1958 from Pyrah to Sir George Martin, Chairman of the Board of Governors robustly states his position (Pyrah Personalia, University of Leeds Archive; no response is extant):

> "I heard a day or two ago that the Artificial Kidney was to be televised and that definitive steps have already been taken by Professor Tunbridge to do some preliminary recording and script…Leaving out of account…the desirability of making these broadcasts…I think it is unfortunate that Professor Tunbridge has arranged it in the way he has, without prior consultation…I should have thought it would have been sufficient for Dr Fletcher…to have done the introduction and for Doctors Parsons and McCracken to work the machine. If any senior person in Leeds was wanted, I think the head of the Department concerned, namely myself, should have been given the opportunity of it. However, I am not really keen to do this but I think it would be unfortunate if the broadcast was done by someone not directly concerned with the Department of Urological Surgery."

[184] Medical attitudes changed so that the second series of YLITH (1961) was fully supported by the profession and was even introduced by Sir Arthur Porritt, President of both the Royal College of Surgeons and the BMA

Despite the tetchiness of the medical in-fighting, the programme entitled "Machinery for Living" was successfully broadcast on the evening of 8th April 1958. The tightly scripted programme was introduced by Charles Fletcher and Ronald Tunbridge and featured Parsons with the artificial kidney and Geoffrey Wooler[185] with a cardiopulmonary bypass machine. Consistent with the YLITH format, the programme was an amalgam of pre-recorded 35mm film sequences inserted into a live outside broadcast, the format being dictated by the available technology (Karpf 1988)[186]. A copy of the actual typewritten script was retained by the cardiothoracic theatre sister and is an Appendix to this chapter. A short sequence of the film used in the programme has also survived and shows Parsons and McCracken operating the haemodialysis machine[187].

YLITH, the prototype for televised medical programmes, has achieved "a mythical quality" (Karpf p12) and established the pattern of successful medical broadcasting: doctor involvement, prestigious hospitals, and success (the patients did not die). This popular documentary featured only doctors and reading of the surviving script endorses Karpf's statement that "the medical approach validates experts, especially the expertise of the doctor, and the visual grammar of medical programmes tends to reinforce the doctor's centrality and authority…The medical gaze prevails." That the medical centrality was a deliberate ploy by the makers of the programmes is evidenced by their deferential attitude: the producer, Bill Duncalf, spoke of "superior race of beings whose calling raises them from the ordinary level of human fellowship" (Karpf 1988 p53). The deferential attitude, typical of the time, was also displayed by the patients who, to later eyes, appear reticent and anxious, perhaps overawed as much by the new technology of television as by the high-tech medicine (Boon 2011).

It is clear from the script that the Leeds medical staff utilised the opportunity to promote both their institution and themselves. It is not possible to measure the impact of the broadcast, but it is not unreasonable to suggest that the LGI was established, at least in the public's eye, as the leading renal centre of the day. Certainly the event continued

[185] Wooler was a distinguished and innovative cardiothoracic surgeon at the LGI. Wooler, G. (1999). Pig in a Suitcase. Otley, Smith Settle.

[186] According to Boon (2011) it later became known that significant problems had occurred following the filming of the cardiac operations in March 1958. Two of the featured patients died in the postoperative period and it was decided that it would be improper to use the recorded footage. Both the LGI and the BBC wanted to use live film of the surgery, but the bypass technician became ill and in the end the programme used a mock-up

[187] The script was passed to Ms Freda Ellis, sometime sister on the Professorial medical ward responsible for the renal patients, to whom I am indebted. I am grateful to Mr David Hamilton who gave me the video.

to resonate with the staff for many years, and they saw the showcasing of the LGI as a vindication of what they perceived as their pioneering work.

6.5 Patients[188]

At the onset there could have been no idea of future demand for dialysis, nor where the patients would come from. The LGI, being the largest hospital in northern England, might be expected to generate some candidates for dialysis, most probably from its department of urology. There is good reason to believe that there had been no assessment of the numbers of patients with ARF in Leeds other than those with urological problems, and there is little evidence that even these had been systematically recorded and analysed. Parsons' memoir gives no suggestion that either he or Pyrah had any regular or even sporadic involvement in the management of uraemic patients in other departments in the LGI or in hospitals in Leeds (St James's, Chapel Allerton, Ida, Maternity, Women's). There is no way of knowing whether there were established, albeit informal, referral pathways to the teaching hospital from elsewhere in, for instance, the West Yorkshire conurbation. The data simply no longer exists, if it ever did. The Leeds Professorial medical unit, like most such academic departments, investigated the physiology of metabolic disorders, but this was directed towards diabetes and endocrinology and there was no particular interest in the kidney which might have attracted patients from elsewhere[189].

Papers from the Hammersmith, which would have been the sole British source of reference, gave no indication of the catchment area served by that hospital nor of the selection of patients for inclusion in the published work. The movement towards an international classification of disease, which became the basis for recording activity in hospitals throughout the NHS, was in its infancy and very incomplete. There appears to have been an overall impression that ARF was uncommon, an impression reinforced by its occurrence across the spectrum of medical activity so that an individual surgeon, physician or obstetrician would have but occasional contact with such cases. It may well be that the assumed relative rarity of treatable ARF was the rationale behind the MRC's lukewarm endorsement of the proposal for a dialysis machine at Leeds, rather than a reluctance to espouse new technology.

[188] The changing demography and natural history of ARF in the second half of the 20th century is considered in a later chapter.

[189] When Christopher Blagg was appointed lecturer it was to study thyroid disease with specific responsibility for the administration of radio-iodine. Brian McCracken had researched thyroid disease in the USA. Other Leeds academics of the time included Monty Losowsky (liver disease) and Verna Wright (rheumatology).

The reality proved much different: the single machine, manned by essentially part-time medical and nursing staff (all had, at least nominally, other commitments), became overwhelmed by the demand for treatment and the numbers of patients. This theme of the pressure on staff and facilities became a recurrent issue in the correspondence with the various financing authorities. It must be assumed that in addition to George Godber's contact with hospitals in the northern half of the UK, there was an informal personal network which ensured that patients from north of the Trent were referred to Leeds.

6.5a Origin of referrals

Table 6.3 shows the region from which patients who were dialysed at the LGI were referred. There were certainly others who did not receive treatment on the artificial kidney but were managed conservatively, but records are incomplete. The renal unit notebooks include records of 23 patients in 1956/7 who were referred for dialysis but did not receive it. Five were moribund on arrival and died within a few minutes or hours. Several were obviously considered unsuitable for treatment either because of their general condition or because of inoperable malignancy. Only two came from Leeds (not LGI), the rest being from the same catchment area as those who were dialysed. Of the 14 whose conservative treatment is documented, only two died; 7 had obstetric ARF, 3 transfusion reactions, one was dehydrated and one had calculus anuria which was relieved by surgery by Professor Pyrah. This admittedly incomplete series is of interest in that it suggests that at least in the early days a quarter of referrals were correctly assessed as being manageable by conservative therapy alone, with a mortality of about 15%. It also demonstrates that the Leeds group quickly became adept at the total management of the uraemic patient and did not restrict themselves to simply applying the machine. These cases were important in leading Parsons and colleagues to develop indications for dialysis on top of medical management (Parsons, Hobson et al. 1961). Further, such patients were comparable in severity to those published by Bull from the Hammersmith and clearly reflected the milder end of the spectrum of ARF, suitable for non-dialytic therapy.

Analysable records of some 700 dialysed patients from 1956 to 1965 show that around a third[190] were referred from within the Leeds hospitals (some may have been domiciled outside Leeds, the move to renal treatment being the final step in a complex,

[190] This proportion treated by the LGI renal unit remained remarkably constant. From 1983 to 2005, 60 – 70% of the patients came from outside Leeds. That the number remained high despite the opening of other units across Yorkshire reflected the LGI's continuing role as a regional referral centre for all specialties.

but unrecorded, referral pathway). The remainder came from almost anywhere north of the river Trent, which is effectively the halfway point in the UK. The numbers from outside Leeds rose in the early years, presumably as word of the service spread. The referral pattern changed with time: there was a rise and subsequent fall in referrals from distant centres as facilities became available, initially in Newcastle and then progressively in the major cities of northern Britain. There was a disproportionate number of urological cases (lower urinary obstruction from stones or malignancy) from Leeds, reflecting the importance of the urological service

REFERRING REGION	**1956/7**	**58**	**59**	**60**	**61**	**62**	**63**	**64**	**65**	**56-65**
LEEDS	30	19	27	32	40	30	30	29	33	30
WEST YORKSHIRE	17	10	9	14	11	16	32	35	29	18
SOUTH YORKS (Sheffield)	6	9	12	16	17	27.5	11	5	2	13
NORTH YORKS	3	9	5	5	11	2.5	10	12	13	7
HUMBERSIDE	8	4	8	6	3	2.5	6.5	10	13	6
NEWCASTLE + NE	20	15	4	-	-	-	-	-	-	4
WEST MIDLANDS (Birmingham)	1.5	2.5	5	5	1	-	-	-	-	2
EAST MIDLANDS (Leicester, Nottingham, Derby)	4	1.25	11	13	17	20	7.5	2	4	10
LIVERPOOL + NW	3	6.3	7	1	-	-	-	1	4	2
MANCHESTER (Lancashire, Cheshire)	4	14	9	8	-	1.25	2	3.5	-	5
SCOTLAND	4	10	1.3	-	-	-	-	-	-	2
OTHER	-	-	1.3	1	-	-	1	1.7	-	0.6

Table 6.3. Region of referral of dialysis patients (%), 1956 - 1962

The distances involved created logistic difficulties. Most patients were transferred by ambulance with an escorting doctor and nurse. Helicopters were used very occasionally, but an ambulance was required for the final stages as the LGI did not at that time have an integral helipad. The state of the roads and the comparatively basic equipment in the ambulances meant that transfers were lengthy and carried considerable risk for these precarious patients. Transfer by train was not infrequent as it was more efficient across long distances (Turney 1999). From Scotland, the transfer was by the overnight sleeper: one compartment was reserved for the patient, another for the attending staff. Even this

was not without difficulty: as the *Yorkshire Post* breathlessly reported, the condition of a patient en route from London to Leeds on the "White Rose Express" in 1963 (for a transplant) deteriorated so that her attendants threw a message from the window as the train passed through Doncaster. The message was relayed to Wakefield, where the train was met by the "Corporation ambulance", in which she safely completed her journey to the LGI. The cost of transfers was borne by the referring hospital.

The widespread origin of the patients is a measure of the previously unmet demand for dialysis for ARF. The unpredicted success of Leeds in attracting these patients nearly proved its undoing by swamping staff and facilities. There is no record of whether or how many referrals were turned away because of lack of space at the LGI.

6.5b Transplantation and end-stage renal failure

On 14th February 1963 a press conference was held at Leeds General Infirmary. Frank Parsons, FP Raper (urologist) and Sir Donald Kaberry MP (Chairman of the Board of Governors) announced that the first[191] ever cadaveric renal transplant had been performed 66 days previously, that the recipient was doing well and would shortly be discharged from hospital. This astonishing event made headline news which spread throughout the world[192]. As an example, *The Daily Telegraph* devoted more than half its front page of 15.02.63 to a detailed report, with follow-up reports and comment in the ensuing days. The excitement was due to the potential of transplantation to offer a "cure" for untreatable end-stage renal failure. The LGI conducted a rather skilful PR campaign with frequent press releases and photographs of the recipient, usually accompanied by a nurse in full dress uniform with the unique hospital architecture in the background. Public interest did not wane: the recipient made many appearances in the press and on television doing "normal" things (such as watching Leeds United at Elland Road) throughout the 18 months that he lived, his passing receiving prominent attention in both

[191] It later became known that this was in fact the second or third attempt at allografting in Leeds, the first having been an unmitigated disaster. A 30 year old woman had developed ARF as a result of eclampsia and antepartum haemorrhage. The failure of recovery of renal function after several dialyses and a renal biopsy showed that she had irrecoverable acute cortical necrosis. Out of desperation, and with the patient in advanced uraemia, it was decided to perform a renal transplant. She received two doses of total body irradiation and the transplant was performed on 12.07.1959, the donor having died in the LGI neurosurgical unit from a cerebral haemorrhage. Unfortunately, the recipient suffered a cardiac arrest on induction of anaesthesia (presumably because of her metabolic state) and, although resuscitated, never regained consciousness and died of overwhelming sepsis three days later, the graft never having functioned. A further unsuccessful transplant receives brief mention in a later paper Parsons, F. M., M. Fox, et al. (1966). "Cyclophosphamide in renal homotransplantation." Brit Med J **38**: 673-676. but no other record can be found.

[192] The public impact can be measured by a, possibly apocryphal, story that a letter from a well-wisher in Australia was safely delivered by the Royal Mail despite bearing the simple address "Peter Lucas, Leeds, England".

national and local media. The enthusiastically uncritical media response to transplantation reached its apogee later in the decade with the intense global coverage of the first cardiac transplants, for which the surgeons in both South Africa and Britain actively participated in and perhaps manipulated the publicity (Nathoo 2009).

The event was astonishing because of the technical and intellectual problems: not only surgical difficulties and lack of useful immunosuppressive drugs[193] but also, despite the work of Medawar and others, only a sketchy understanding of tissue-typing and the immunological process of graft rejection. When the Peter Bent Brigham had started transplantation in the 1950s (Merrill, Murray et al. 1956; Murray, Merrill et al. 1958; Merrill, Murray et al. 1960), the problem of donor incompatibility was circumvented by taking advantage of the very rare opportunity presented by identical twins. Later, they performed skin grafts from potential live-related donors. If the skin appeared not to be rejected, it was assumed that the kidney graft would succeed: truly a perilous experiment (Fox 1998; Fox and Swazey 2002). The high risk of rejection of a transplant from an unrelated cadaveric donor (and lack of procedures for the pre-treatment of the donor and preservation of the kidney during the 'warm' and 'cold' ischaemia time) had discouraged further experimentation. At Leeds, the department of urology conducted a series of studies of the effects of uraemia and drugs on the rejection of rabbit skin allografts and Parsons was interested in solutions for the perfusion and preservation of kidneys prior to transplantation (Parsons, Markland et al. 1963; Parsons, Fox et al. 1966; Carruthers, Clark et al. 1967; Carruthers, Clark et al. 1969; Carruthers, Clark et al. 1969).

Despite questioning some of those intimately involved, it is not possible to know exactly what circumstances gave Leeds the confidence to embark on transplantation, which continued for a decade or so at the LGI. The programme was disrupted by the sudden death of Fred Raper and really only resumed with the appointment of Geoffrey Giles, who had gone from Leeds to Pittsburgh to train with Starzl, as Professor of Surgery at St James's Hospital. A number of urology trainees established transplantation when they were appointed elsewhere, for example Sheffield.

[193] At the time the immune response was suppressed by (potentially lethal) irradiation of the recipient and graft and then high-dose corticosteroids and a noxious anti-cancer drug, actinomycin D. Leeds later published on the use of another chemotherapeutic agent (cyclophosphamide) Parsons, F. M., C. Markland, et al. (1963). "Cadaveric renal transplantation." Brit Med J **1**: 930-931, Parsons, F. M., M. Fox, et al. (1966). "Cyclophosphamide in renal homotransplantation." Ibid. **38**: 673-676. but at the same time (Sir) Roy Calne at Cambridge was developing the use of the less toxic but equally effective azathioprine, a product of the Wellcome research programme on folic acid.

Although Leeds transplanted a number of patients, referred from around the country, with reasonable success, perhaps the most significant consequence of Leeds' initiative was the establishment of the European registry. The importance of registries in establishing the identity of specialties, stimulating communication and discussion, and influencing practice and results has previously been discussed. The innovation by Leeds in which methods and results were shared and analysed rapidly proved the value of registries by showing, for example, the importance of surgical technique, immunosuppressive regime, and the condition of the recipient (Disney 1998). Initially, Parsons and Philip Clark (then senior registrar in urology) made informal enquiries to, and collated the results from the few interested centres across Europe (Parsons and Clark 1965). This quickly became formalised into the registry of transplant activity and this, together with the parallel dialysis registry initiated by Parsons and Drukker, formed the nucleus around which the European Dialysis and Transplant Association was created. The establishment of the European registries could perhaps be regarded as Parsons' lasting achievement: they were eventually copied nationally and internationally, not only in nephrology but across many fields of medical endeavour. Parsons remained for many years an editor of the annual registry reports which did more than merely tabulate activity but also analysed results, complications and treatments(Parsons and Clark 1966; Clark and Parsons 1967; Parsons and Clark 1968; Parsons and Clark 1969; Parsons, Clark et al. 1970; Brunner, Gurland et al. 1971; Parsons, Brunner et al. 1971; Gurland, Brunner et al. 1973; Scharer, Brunner et al. 1973; Parsons, Brunner et al. 1974; Brunner, Giesecke et al. 1975; Scharer, Chantler et al. 1975). The EDTA not only provided an international forum at a time when numbers of renal specialists in any country were relatively few but also a credible association for those practicing the 'craft' of dialysis and transplantation who had experienced difficulty in gaining acceptance into more 'scientific' associations.

6.6 Problems and solutions

There is no evidence that any of those involved in the initiation of dialysis at Leeds gave any thought to the potential consequences of their actions. That Parsons was given a 'blank cheque' was true both financially and metaphorically. Patients with renal failure absorb huge costs: staffing, accommodation, drugs and diet, dialysis, investigations, complications. With the sole exception of correspondence with the MRC about ancillary staff, there was never any attempt to cost the activities related to dialysis. This was not out of the ordinary: there appears to have been little or no attempt at costing throughout

the NHS for many years (Webster 1988; Cutler 2003; Cutler 2006) and perhaps even still. The doctors at the LGI were in the comfortably privileged position of never having to consider expense: a wealthy hospital with considerable endowment funds which could be used to underwrite clinical activities as surreptitious support of the NHS, and the relatively generous central funding of the teaching hospitals. The accelerating managerial involvement after the 1974 NHS reforms was not only unforeseen but also alien to the post-war generation of doctors. The staff at the LGI appears not to have been called upon to account for their activities or even to have considered doing so. The huge expense of dialysis was simply not an issue in the early days of its use, although it later became contentious worldwide.

In only one respect, the perennial conflict over beds, did Parsons and Pyrah personally attempt to enhance their facilities, as previously alluded to. When dialysis started in September 1956 there would have been no way to forecast demand. This demand from large numbers of patients referred from far and wide rapidly overwhelmed the informal allocation of two beds on the Metabolic Ward for renal patients. In just over three years of the late 1950s, more than 200 patients were dialysed (Table 6.4), and an unknown number with other renal problems cared for.

The epidemiology of ARF will be discussed later in the context of the consequences of the changes in the disease, but suffice it to say that the patients in the 1950s were notably young. This was because of the preponderance of obstetric cases (20-30% of the total, up to 50% of the females) and because the referral distances meant that only selected fitter patients were suitable for transfer, the transfer often depending on public transport.

Period	n	Median age	% mortality
1956-9	203	42.0y	48.8
1960-9	576	47.0y	49.5
1970-9	168	60.0y	38.6
1980-9	398	60.2y	50.8

Modified from (Turney, Marshall et al. 1990)

Table 6.4. Numbers, ages and mortality of ARF patients at Leeds, 1956 – 1989

The outcome in terms of actuarial one-year survival was as good or better than that reported by any other unit before and since, again positively influenced by patient selection. Also notable, and relevant to the future, was the lack of impact on patient

numbers of the opening of other units across the country. Success in recruiting patients created pressures, especially on staff and facilities. This pressure was exacerbated by the length of stay, often weeks, before patients were well enough to be transferred back to the referring hospitals. The length of the dialysis procedure and the need for constant supervision of the machine and patient meant that treatments were performed day and night, the same members of staff also providing the care of the patients on the ward.

Parsons and his team rapidly learnt that ARF is a complex situation requiring complicated management skills, as had been emphasised by Merrill[194]. Following what must have been a very steep learning curve, the Leeds group developed a *modus operandi* which at least made the situation tolerable, produced good results, and set the pattern for future renal practice elsewhere: they created a 'unit' focused on the machine and its supplicant patients. It immediately became apparent that the day to day management of these very ill individuals fell within the purview of physicians, not surgeons: lecturers from the academic department of medicine (Brian McCracken, Michael Moriarty, Christopher R Blagg, and others) cared for the patients, their diet, drugs, infections and other complications. Parsons, supported by these physicians and the urological surgery staff, led on the technical aspects of dialysis. A defined group of skilled selected nurses moved seamlessly with the patient between ward and machine. Technical support was provided by dedicated biochemists and machine technicians. These various groups worked in unison, each having a defined but overlapping role within the whole endeavour. It is improbable that this responsibility-sharing arrangement of cooperative working was pre-planned, but rather it evolved in response to new and changing circumstances and the product was a new way of delivering health care. The traditional hierarchical system of compartmentalised professional groups had been superseded by an integrated team self-sufficiently independent of the host institution of which they were part. This model became replicated as other discrete hospital units (ICU, coronary care, etc) came into being in response to changing technology and practice, not by self-aware emulation but rather by a process of convergent evolution. Thus the 21st century hospital is a syncytium of hermetically sealed clinical units, interacting at the edges but complete unto themselves; households within a village.

Other adaptations to the challenges posed by the numbers and severity of the patients were deliberate. In conjunction with the University department of medical physics,

[194] "We have learnt from bitter experience that, more frequently than not, acute renal insufficiency is not an uncomplicated syndrome. Merrill 1952, p24.

Parsons modified the Brigham-Kolff machine to increase its efficiency in terms of solute clearance, thereby reducing the need for frequent and prolonged dialyses (Lawrance 1983)[195]. There were other more subtle manoeuvres that demonstrated a therapeutic sophistication born of rapidly accumulating experience: a fully holistic approach integrating medical management, diet and dialysis; and the prompt identification of those requiring early and frequent dialysis, stratifying risk of complications and poor outcome on blood biochemistry and clinical status (Parsons, Hobson et al. 1961) (it is perhaps noteworthy that the second author of this paper was the unit's biochemist).

Parsons' repeated references to modifications of the dialyser's performance suggest the centrality of the machine to his way of thinking: management of renal failure, and hence all the activities of the unit, revolved around the device, which determined behaviours and practice. In Leeds, and to a great extent elsewhere, the technology that had first been justified by the disease came to control and, hence to limit, the response to it. Clinical problems were seen as technical failures and the reaction was seen through the narrow prism of technical solutions. This attitude, perhaps not surprisingly in a specialty defined by and wedded to a procedure, persisted indefinitely: the machine was the 'cure' for the particular ill; if the patient succumbed then the treatment must have been in some way inadequate. Therefore, in this restricted logic, if the machine could be induced to perform better the outcomes would inevitably improve. The centrality of the machine excluded alternative or additional interventions and responses. One response was **not** the acceptance that the technology was only a part, and perhaps only a small part, of the answer despite accumulating evidence that the progressive refinement of the machine exactly paralleled the declining clinical outcomes of later years. For the biomedicalised practitioners (Clarke, Shim et al. 2003), technology gained ascendancy over the disordered patient. The orientation of practice towards exclusively technical solutions had considerable impact on the later treatment of ARF.

6.6a Diagnosing chronic renal failure

Opening the doors to all comers inevitably put Leeds at risk of accepting not only clear-cut recoverable ARF but also those with irreversible chronic renal failure who either presented late or who had untreatable acute renal parenchymal disease

[195] Parsons in an interview gave this justification for increasing the capacity of the dialysis machine (Lawrance 1983): "Self preservation was the main motive drive in increasing the dialysing area to 2.8m^2 and blood flow rates to 500 ml/min. This achieved a huge clearance…so that even in very severe catabolic patients dialysis was only required on alternate days. A daily dialysis, with the parish more or less the size of the UK, would not have been possible with our work load."

(glomerulonephritis)[196]. In some cases the referral would have been precipitated solely by the finding of a raised urea without a clear history and diagnosis.

YEAR	% CRF
1956/7	18
1958	28
1959	23
1960	31
1961	36
1962	41
1963	37
1964	31
1965	16
1956 – 1965	30

Fig 6.5. Chronic Renal Failure Patients (%) Treated by Dialysis

Overall 30% of new patients in 1956 – 1965 presented with irreversible chronic renal failure (Table 6.5). These figures refer only to those who received at least one haemodialysis session; there may well have been others in whom the diagnosis was made before dialysis was instituted and so were not offered treatment. In some cases, dialysis was used as temporary palliation of symptoms to allow the patient to return home or to the referring hospital to await the inevitable outcome. Dialysis was invariably withdrawn as soon as the diagnosis of ESRD was established. Policy gradually changed during the 1960s as it became technically feasible to provide long-term treatment by peritoneal or haemodialysis. In the mid-1960s a particular situation obtained in Leeds: patients with ESRD were accepted for transplantation and were supported by dialysis until a transplant could be performed. It is unclear how long dialysis was offered for before it was decided whether a suitable donor kidney would or would not be forthcoming. Additionally, dialysis appears not to have been extensively used post-transplant. Survival was predicated on the opportunity and success of the graft.

With no means of indefinitely sustaining life by dialysis, nephrologists were faced with several unpalatable options in this group in whom the diagnosis was uncertain: refusal to accept any but the most obvious ARF or acceptance of all whom they believed

[196] Even in recent years about half the patients with slowly progressive end-stage renal failure require maintenance dialysis within one month of first medical contact.

might ‘benefit’ from dialysis by recovery of renal function or symptomatic improvement. It is, to say the least, unsatisfactory (ethically, emotionally, and in terms of resources) to withdraw treatment after one or several dialyses from a patient in whom it becomes apparent that there is little or no expectation of restoration of independent life. It is also relevant that aggressive immunosuppressive therapy for rapidly progressive glomerulonephritis did not appear until two or more decades later, after the various categories of renal disease had been identified.

Practitioners were therefore presented with the dilemma of how to obtain a prompt accurate diagnosis from which prognosis would flow. By their espousal of complex invasive technological intervention they had rejected the established view that advanced uraemia was almost inevitably fatal, suitable only for medical and nursing palliative care. But this optimistic view could not be sustained in the face of irrecoverable renal failure, for which their technology proved inadequate. It was therefore imperative to rapidly and unequivocally reach a diagnosis to determine prognosis and hence whether to offer treatment. But therein lay a problem: the available diagnostic techniques, exclusively radiological, were inadequate for purpose. Ureteric catheterisation and retrograde pyelography would demonstrate obstruction and occasionally relieve it; plain abdominal X-rays might show shrunken kidneys or calcification; and renal shape and size might be demonstrated by intravenous pyelography (IVU), which works poorly if at all in advanced uraemia. Serological tests for the, as yet unidentified, autoimmune diseases of the kidney did not exist. Practitioners were therefore dependent on renal histology, but this dependence created its own problems: how to obtain an adequate sample of kidney tissue, and then how to interpret the microscopical appearances. Initially, wedge biopsies were obtained by open surgery, itself problematic in metabolically deranged patients at risk of haemorrhage because of renal failure and heparinisation during dialysis. Percutaneous needle biopsy was introduced into Leeds by Christopher Blagg from 1958, teaching himself the technique after verbal instruction from James Robson in Edinburgh (CR Blagg, *pers comm.* 20.10.2010). Interpretation of the histological appearances was far from straightforward because the wide range of glomerular diseases had been neither described nor agreed. In short, the situation was confused and confusing and still struggling out of the constraints imposed by the Ellis revision of ‘Bright’s disease’ (Ellis 1942; Peitzman 1989). Renal histology had received little attention, mainly because of the paucity of vital material, and there was no cadre of experienced pathologists. So at Leeds a middle-grade pathologist, Keith Anderson, was

given the role of 'renal' pathologist and he rapidly became a leading, but initially autodidactic, authority in the field.

6.6b Nosocomial infection

The final problem that exercised the Leeds unit, and indeed nearly forced its closure, was hospital-acquired (nosocomial) infection. Multiresistant microbial infections were not, of course, a problem before the advent of antibiotic chemotherapy and indeed there is no way of knowing whether they actually existed. Some bacteria are capable of producing enzymes which destroy or interfere with the actions of antibiotics, thereby conferring resistance to chemotherapy. Penicillin-resistant *Staphylococcus aureus* was first detected in 1947, just a few short years after its first use, and thereafter with increasing frequency worldwide (Bud 2006; Bud 2007). Until the 1960s *S aureus* was the main cause of nosocomial (hospital-acquired) infection, being overtaken by gram-negative organisms until the 1990s when it regained its dominant position globally (John and Barg 2004). Throughout the 1960s it was far and away the greatest cause of infection of the Scribner dialysis shunts. By the late 1950s a number of broad-spectrum antibiotics were freely available and freely used, with overall beneficial effect. However, from around 1957 there appeared the 'first' problems with hospital-acquired multiply-(methicillin-) resistant *S aureus* ('MRSA'), first detected in Britain (Hartstein, Sebastian et al. 2004), against which no available drug was effective.

Renal patients are now known to be particularly susceptible to nosocomial infection: uraemia suppresses the immune response, they have long in-patient stay which increases contact with other infected patients or asymptomatic 'carriers' among the staff, themselves a closed coterie at risk of cross-infection. Additionally, frequent invasive procedures, general debility and widespread use of antibiotics all contribute to risk, which is exacerbated by the importation of organisms from other hospitals. In the period in question, the strict fluid restriction encouraged oropharyngeal sepsis, particularly colonisation by *Candida*.

As a result of all these factors, there were a number of cases of nosocomial staphylococcal infection with a high mortality. The problem was aired in a letter, dated 18.09.57, from Pyrah to the MRC in which he makes his first reference to dialysis after the unit was set up. To support his case for facilities "of a special kind" for renal, he marshalled a number of arguments, including 7 cases of hospital-acquired staphylococcal enteritis (an unusual complication), of who 6 had died and "at least 4 of which were in recovery" from ARF. He notes: "These resistant organisms seem to be

everywhere, including blankets, bed clothes, and nurses' throats". He advances this as justification for the provision of special treatment rooms for the artificial kidney and its patients. However, by concentrating on the clinical service activities and its problems, Pyrah somewhat defeated his argument with the MRC, a research organisation. It is not unreasonable to date the cooling of relationships between the MRC and the LGI from these exchanges.

The unit faced an obvious dilemma: should they continue to accept patients in the knowledge that at least some could be prejudiced simply by being admitted. The solution was a re-think of how the unit was managed: isolating patients in single rooms, restricting the indiscriminate use of antibiotics, obsessive attention to cleanliness, enforcing aseptic procedures, and increasing the intensity of dialysis in the belief that reducing the degree of uraemia would enhance natural resistance to infection. (Other workers later confirmed that increasing the 'dose' of dialysis did in fact reduce the number and severity of complications, including sepsis (Teschan, Baxter et al. 1960; Kleinknecht and Ganeval 1973)). The Leeds unit devised effective preventative measures that had to be re-learnt decades later when MRSA and other hospital-acquired infections again proved troublesome. One cannot help reflecting not only that the history of medicine is scattered with examples of the enforced re-learning of basic lessons painfully acquired by earlier generations but also that the Leeds unit (and, presumably, other early renal departments) were constrained to feel their way to solutions by a combination of careful informed thought and pragmatic empiricism.

6.7 Conclusions

In 1956 Parsons and his colleagues embarked on an adventure across uncharted territory. They wrote the rule-book for their project and they displayed ingenuity, intelligence and perseverance which caused their enterprise to be labelled a success. That this occurred in an industrial city in northern England was due to a concatenation of factors which included a privileged wealthy independent-minded institution and the support of a number of authorities. They confirmed the utility of a technology which, despite the difficulties with its use, fulfilled a previously unmet, and increasing, demand which they had uncovered. Leeds provided an example followed by other centres throughout the UK.

6.8 Addendum to Chapter 6

Script of "Your Life in Their Hands" 08.04.1958

Donated by Ms Freda Ellis, formerly Sister of the Professorial Medical ward, LGI.
(Note: "Wurmser" refers to ingenious animated diagrams by Alfred Wurmser, A BBC graphics artist. These were drawings on large boards with hidden levers that could move sections of the diagrams to illustrate anatomical and other medical points (Essex-Lopestri 2006)).

VISION	SOUND
SEQUENCE I - HAMMERSMITH	
Dr Fletcher	Dr. Fletcher introduces ninth programme and hands over to "Professor of Medicine at Leeds General Infirmary".
SWITCH TO LEEDS OB	
SEQUENCE 2 – THEATRE 3	
2. IN CORRIDOR Track into Th. 3 to Professor Tunbridge	<u>Professor Tunbridge</u> Good evening and welcome to the General Infirmary at Leeds. The Infirmary was founded in 1767 by William Hey, a famous surgeon of the period.
3. Designer's drawing	The present hospital was designed by Sir Gilbert Scott in 1864 and here is a copy of his drawing.
2. Professor Tunbridge	It was one of the first hospitals in this country to be built in the pavilion style. The hospital has had many distinguished surgeons and physicians and one name at least will be familiar to many of the senior viewers – Lord Moynihan. Dr. Thackrah played an important part in the founding in 1831 of the Leeds School of Medicine but is perhaps better known for his book "The Effects of Arts, Trade and Professions on Health and Longevity", a copy of which I hold, which lead to his being called the father of industrial medicine. Another of the distinguished physicians, Sir Clifford Albutt, invented the short clinical thermometer with which you are all familiar.
3. Caption: Present hospital	After nearly 200 years of continuous service it is perhaps the busiest teaching hospital in this country, yet despite the heavy burden of routine the staff have continued to make advancements
2. Professor Tunbridge	in medical knowledge and in our programme tonight we are going to illustrate some of the pioneer work going on this hospital at the moment.
3. WURMSER 1 (blood circulation)	You all know that blood circulates in blood vessels all over the body. It is pumped there by the heart through arteries and returns by veins. You may remember from an earlier programme in the series that the right side receives blood from the body, and pumps it into the lungs, where it picks up oxygen. It is then returned to the left side of the heart from where it is pumped to

2. Professor Tunbridge Pan to Dr Parsons	all parts of the body except the lungs and then returns to the right side of the heart once again. All tissues require blood but some parts of the body are more vital than others. For instance the brain, which controls the heart and lungs must always receive adequate amounts of blood. So also must the kidneys. Tonight we are going to show you two machines which have been developed for the treatment of patients who have certain diseases of the kidneys, or who have been born with an abnormal heart. These machines are, in effect, an artificial kidney and an artificial heart and lung. Let's deal with the artificial kidney first. For this I hand you over to a member of our Urological Department.
SEQUENCE 3 – THEATRE 3	
2. Dr Parsons Interview 3. CU PATIENT 2. Dr Parsons	Dr Parsons: Good evening. The function of the kidney is complex. In simple terms they remove waste materials from the blood. They also eliminate substances that are eaten in excess of the body's requirements. In certain conditions the kidneys cease to work for a period of time which may last for 5 to 30 days. When this occurs the diet has to be restricted to glucose, water and vitamins. The living processes of the body continue to form waste materials and these accumulate in the blood and may reach levels that endanger life before the patient's kidneys start working again. Such a situation occurred in this patient. Mr. Gudor had a motorcycle accident and received a fractured skull and multiple fractures of the pelvis bones. This caused severe shock which in turn affected his kidneys and they ceased to work for nearly 30 days. Good evening Mr. Gudor. When was your accident? 6 months ago. He doesn't remember coming to us from Halifax as he had also severe concussion as a result of the fractured skull received in the accident. Following the accident, what was the first thing you can remember? He came to us 6 days after his injury but by this time the waste material had accumulated in his blood to extremely dangerous levels. We were able to remove these waste materials by means of the Artificial Kidney, and he improved considerably. So severe was the injury that a further 3 treatments were required on the Artificial Kidney before his kidneys started to work. From then on he made a rapid recovery. To Gudor: Are you working now? What is your work? Thank you for coming back. That is a typical example of the use of the artificial kidney. Now let us turn to the machine itself.

2. Dr Parsons – "wrist" 3. Wurmser 3 2. Dr Parsons – cellophane 3. Wurmser (2 go wider) 2. Dr Parsons	Like the normal kidney it removes waste material from the blood and to get it to work we have to by-pass some of the patient's blood through the machine. Just above the wrist, in this position, is an artery which you can feel pulsating. We expose this artery and insert a tube into it. The blood from the patient flows through this tube to the Artificial Kidney as seen on this diagram. There the blood enters a special type of tubing made of cellophane. Here is a small sample of the cellophane tubing, and 160 ft. are wound onto a large drum. This is immersed in a large tank of fluid. This cellophane tube is porous to the waste materials and also to essential materials in the blood. These substances in the blood will only pass through the walls of the cellophane tube if they are in greater amounts in the blood than in the fluid outside. The waste materials pass from the blood into the bath, but the essential materials or chemicals are added to the bath so that these are not removed by the Artificial Kidney. The blood as it leaves the machine, has been purified and it is pumped into a reservoir which acts as a trap and filter. It then flows back into the patient's own circulation through a tube which ahs been inserted into a vein. This process continues for about six hours when the amount of waste materials has been reduced to safe levels. My colleague will now show you the Artificial Kidney.
SEQUENCE 4 – THEATRE 3	
2. Dr McCracken and girl patient 3. 2-SHOT Pan down to drum 2. Dr McCracken 3. CU PUMP, TUBES 2. Dr McCracken, PAN DOWN TO DRUM 3. CU CELLOPHANE BEING WOUND ONTO DRUM Pan down to drum CUE FILM (2 away) (3 onto McCracken) (Dr parsons mic. To Dr Nixon)	FILM CUE: The BBC a few weeks ago made a special film in one of our wards showing a patient under treatment.
SEQUENCE 5. FILM –	00

ARTIFICIAL KIDNEY	
Film (1'20")	Film
CU of tubing being wound	Commentary: The coils of cellophane tubing are wound onto the drum…..
End of first part Instruments in case CU Dr. Patient across bed showing patient's face and doctor CU drum going round	Commentary: …..finally the machine is primed with blood. 1'20
GAP IN KIDNEY FILM (30") 3. Dr McCracken	Dr McCracken 1'50"
PART 2 OF KIDNEY FILM (1'10") FILM Wide shot of room	FILM Commentary: The doctor at the patient's side….
End of second part Wide shot of room showing machine and patient CU pump Wide. Doctor enters, checks with nurse, goes out left (7" after he leaves)	Commentary: …..the patient lies peacefully and comfortably in bed and cannot feel anything unusual. 3'00
SEQUENCE 6 – THEATRE 3	
3. Dr Parsons with Mrs Mitchell in chair	Dr Parsons (on stick mic.) The patient you have just seen was treated 3 weeks ago. Her kidneys have started to work again and she is now convalescing. Here she is. Good evening Mrs Mitchell. Good evening sister. Did you feel anything unusual whilst you were being treated on the artificial kidney? You are looking forward to going home? Where do you live? Mrs Mitchell had an unusual complication of pregnancy. She will be going home to Dunbartonshire in about a week.
3. Dr Parsons	In the treatment of patients on the Artificial Kidney we require two pints of blood to fill the machine before it is connected to the patient. Many of these patients require further blood transfusions during their illness as their blood forming organs frequently cease to work. On behalf of these patients and all those we have treated may I say thank you to all those blood donors who have

	made the treatment possible.
SEQUENCE 7 – THEATRE 3	
3. Professor Tunbridge walks in (3 on to Wurmser next)	Professor Tunbridge (on stick mic.) That was one of the two machines I mentioned at the beginning of the programme – machines designed to perform a function which, for some reason, cannot be carried out by the body. Now we come to the second machine. This is used by the Department of Thoracic Surgery and here is one of the members of that Department to tell you about it.
THEATRE 4	
2. Dr Nixon 3. Wurmser 4 2. Dr Nixon 3. Wurmser 4A 2. Dr Nixon (wide) 1. CU machine CUE FILM	Dr Nixon: The second machine – the heart lung machine takes over the work of the heart and lungs and enables the surgeon to operate on the inside of the heart which is then empty of blood. Let's look at the circulation again in diagrammatic form: Dr Nixon commentates: ….back to the tissues of the body. Dr Nixon continues commentary Dr Nixon commentates on machine FILM CUE Dr Nixon: Now in order to show you how the heart lung machine is used in the operating theatre we have prepared a special demonstration film with a commentary by one of our surgeons.
SEQUENCE 8 – HEART AND LUNG MACHINE	00
FILM Start: Wide in anaesthetic room	FILM Commentary: "The patient is brought into the anaesthetic room….
End: MS Machine with instruments (20") Wide shot with Anaesthetist in foreground (7"0) CU machine	Commentary: When this is complete no blood will be circulating thro' the patient's heart which enables it to rest during the operation. 4'30"
SEQUENCE 9 – THEATRE 3	
1. Professor Tunbridge	Professor Tunbridge: As we pointed out the film you have just seen was a demonstration film. I will now pass you over to the surgeon whose voice you heard commentating and he will introduce a patient on whom the heart-lung machine has been used.
THEATRE 4	

2 Mr Wooler Patient walks in	Mr Wooler introduces patient
THEATRE 3	
1. Professor Tunbridge	Professor Tunbridge: This evening you have seen two mechanical aids to living working both the results of many months of research and team work. These developments have been assisted by generous grants from the free moneys of the United Leeds Hospitals and the Nuffield Foundation. Good night from Leeds
SEQUENCE 10 - HAMMERSMITH	
Dr Fletcher	Dr Fletcher: Thanks all those responsible for the presentation of the programme in Leeds Infirmary, winds up, trails next week's programme. Goodnight
3. Roller caption (35") 2. Corridor shot	Music on tape from CCR2 in London

7. SUBSEQUENT TRAJECTORY OF ARF AND ITS TREATMENT: TECHNOLOGY

7.1. Introduction

The development and early dispersal of dialysis was reviewed in Chapter 2, in which two themes emerged. Whatever may have been the intention of the early users of the technology, its limitations rendered it suitable only for ARF, which was itself then defined by its technology. Secondly, dialysis as originally presented was the relatively unsophisticated product of scattered individuals using appropriated technologies. This chapter attempts an overview of what happened next. A novel development is inevitably naïve at its inception and requires a shower of micro-inventions to polish and refine it for widespread use. Dialysis was in limited use for a restricted patient population for some two decades until demand from a different constituency forced the necessary refinements. The critical change was the involvement of industry, both directly in the construction and marketing of dialysis equipment and indirectly by funnelling industrial developments from other fields into healthcare products: most obviously in the application of industrial membranes to dialysis. The chapter will also attempt to show how the technology and the clinical condition redefined each other in an iterative process that continued from the outset of dialysis to the present day. The application of dialysis to renal failure not only had medical and commercial consequences, but also had social effects centred mainly on ownership of the technology and also, as will be explored later, around redefining the syndrome of ARF to comply with changing medical practice.

This chapter attempts to juxtapose concepts and solutions, problems and technical fixes, in the development of dialysis modalities. It then proceeds to discuss the consequences of these changes, in effect how technology continued to define practice. Some concepts (such as the 'middle molecule hypothesis') only became live issues when commercially-driven changes (such as membranes) allowed them to be realistically addressed. Other problems (such as aluminium-toxicity) were unforeseen complications of long term dialysis which provoked a search for causes and solutions. Throughout, the focus was dialysis for ESRD; ARF patients were fellow-travellers to whom ESRD treatment, its modifications and its theoretical concepts were uncritically applied. ARF was no longer the justification for dialysis, as it had been for the first 20 or so years of its existence.

Although ARF certainly did not disappear during the 1960s and 1970s it lost its primacy in the medical view, attention being focused on ESRD and its treatment and on

the flowering specialty of nephrology with its emphasis on, for example, the immunological and histological dissection of glomerulonephritis. As will be discussed in a later chapter, the disorder and its circumstances had changed when attention was perforce refocused on ARF from c1980. That these changes were barely, if at all, recognised at the time is an anomaly requiring further exploration. One possible explanation is that the limited numbers of renal physicians were preoccupied, if not actually overwhelmed, by the rapidly increasing numbers of ESRD patients and the management problems they presented. Additionally, the involvement of industry, entering and then dominating the rapidly growing market in ESRD treatment[197], redefined dialysis technology and this in turn controlled treatment, initially exclusively for ESRD and belatedly for ARF.

A leap of 50 years to the first decade of the 21st century reveals continuity and change in ARF and its treatment. Modern HD machines are sleek, expensive, computerised control mechanisms which, although visually different from the machines of the 1960s, are in fact conceptually identical. They have been refined for the mass application for ESRD treatment, but are efficiently useful for acute patients. PD is rarely used in developed countries but is important elsewhere and differs only in its packaging. The principles of dietary management are unchanged from those of Borst and Bull, the materials being more refined and the efficiency of modern dialysis allowing more liberal and intensive nutrition. The range and efficacy of pharmaceuticals has hugely changed, but in the management of ARF the control of infection and maintenance of fluid balance and cardiovascular stability remain the central therapeutic goals as they have always been. Again, the products have changed but the principles remain constant.

In general, developments in the theory and technology of dialysis were stimulated by the expanding provision of long term dialysis for ESRD, starting slowly in the 1960s and 1970s and gathering momentum thereafter, and were only secondarily applied to the treatment of ARF. The early development and application of dialysis, to about the mid-

[197] The 1972 Medicare Amendment resulted in an explosion in the numbers of American ESRD patients able to access long-term dialysis, having previously been excluded by the cost of treatment. The resultant exponential growth in numbers and costs (Table) ensured that medical and commercial effort was directed almost exclusively to ESRD dialysis (Rothman, D. J. (1997). Beginnings Count: The Technological Imperative in American Health Care. Oxford, Oxford University Press.)

YEAR	NUMBERS ON DIALYSIS	COST ($)
1969	1000	-
1973	10,000	229 Million
1983	65,000	-
1990	150,000	3 Billion

1960s, was a directed response to the needs of acute patients. At least initially, chronic patients on dialysis were not necessarily more numerous than the acutes, but because they required 2 or 3 dialysis sessions weekly for months or years, new ways of organising and thinking about dialysis and modified technologies were required. ARF lost its primacy in the activities of renal units, but benefited when the technologies developed for CRF were applied to its treatment. Among the benefits for ARF patients from the advent of regular intermittent dialysis for ESRD were: improved standards of performance in well organised experienced units; AV shunts allowing repeated and frequent dialysis; requirement for the safety of ESRD patients stimulating improved dialysis monitoring; the transfer of the idea of more frequent dialysis with good dietary intake from chronic to acute patients; improvements in dialyser design resulting in increased efficiency and reduced blood loss; greater care with blood transfusions.

Only in one context would the technology appear to be radically different from that of five decades previously, and that is the systems for continuous dialysis, which are now the most widely used intervention in ARF, for which they were specifically developed. This specific dialytic therapy for ARF was only possible as a result of the commercially-driven introduction of new dialyser membrane materials for ESRD which also demonstrated characteristics that could be utilised for this new treatment.

7.2. Peritoneal dialysis

The methods of dialysis (peritoneal and haemodialysis) developed in the 1940s persist today, but PD has enjoyed varied fortunes and HD has undergone various transformations, the causes and consequences of these being discussed later. Conceptually simple, PD was probably more widely used than HD in the first decade of dialytic intervention in ARF, but rapidly declined in popularity.

Commentators are unclear why HD was generally adopted in preference to PD, if they consider the competition between the technologies at all. If published outcomes are a reliable guide, PD seemed to be more successful in the early 1950s, but there is no record of centres that may have 'dabbled' with the treatment and failed[198]. Infection remains the most frequent and most severe complication of PD, the iatrogenic peritonitis often being fatal, especially in the critically ill patient. It was not until the 1960s that

[198] Cameron 2002, p113: "The deceptive simplicity of the technique may have led many others, who did not publish, to attempt it and fail." The implication of this oft-repeated view is that because PD appears easy, non-specialists are tempted to use it, thereby depriving their occasional patients of the opportunity of referral for specialist, and hence experienced and more successful, care.

Travenol/Baxter entered the market with pre-packaged sterile designed tubing, dialysate solutions and, most importantly, a stylet and cannula for acute peritoneal access ('Trocath', McGraw Laboratories, which is still sometimes used for acute dialysis). Prior to that, equipment had to be prepared on an *ad hoc* basis by adapting available, but not necessarily appropriate, materials. The ready accessibility of commercial products not only facilitated the technique of PD and hence its popularity, but also placed Baxter in a dominant position when the very much larger market for continuous ambulatory peritoneal dialysis (CAPD) for ESRD opened up in the 1980s.

Whilst complications and convenience undoubtedly influenced the decline and later resurgence of PD, social rather than practical factors may have been as significant. PD lacked the kudos and psychological impact of large, expensive, shiny haemodialysis machines so complex that only select initiates could operate them. If a specialty is, at least partially, defined by its technology then PD, which can apparently be performed by anyone, is an unappealing emblem. Charitable and institutional funders are attracted by 'high tech' machines, not 'low tech' plastic tubes and bags.

PD again became popular for the treatment of ARF in the 1960s, although there are no figures for the proportion of patients so treated in this period. The recrudescence of PD may well have been due to service exigencies rather than therapeutic choice – budgetary constraints or the fact that the HD facilities then existing were simply overwhelmed by the demand for the treatment of ESRD patients[199]. That the increased use of PD was simply a mechanism for coping with limited facilities is indicated by the opinion of many that it is not an adequate treatment for the very ill hypercatabolic patients who were appearing during the 1960s and 1970s, and who required continuous PD for days at a time[200].

The possibility arising in the 1960s of indefinite dialysis stimulated the NHS, perhaps uniquely, to provide a network of dialysis centres for ESRD. The provision was, however, based on a hopeless miscalculation of potential costs and demand. Although this underestimation of future demand is a recurrent theme in NHS planning (Cutler

[199] Cameron 2002, p220: "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 demands of…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 the already overstretched dialysis staff to cover."

[200] Cameron 2002, p205: "…in retrospect may have been better treated by haemodialysis – although the mortality remained just as high in such patients, whatever the treatment, and sadly still had not been reduced by the end of the century whatever the treatment used."

2003; Stewart 2008), it must be accepted that those planning had few if any hard facts on which to base their predictions. The concatenation of inadequate facilities, lack of skilled staff and government fiscal restrictions resulted in the marginalisation of ARF by the overwhelming demands of ESRD. There would therefore appear to be inevitability in the increased use of PD[201] at that time. Nephrologists generally considered that PD provided sub-optimal treatment for many (most?) acute patients, but there appears to have been little public debate of this opinion at that time (Cameron, Ogg et al. 1967; Flynn 1967; Kennedy, Luke et al. 1967). The few reports (Burns, Henderson et al. 1962; Stewart, Tuckwell et al. 1966; Cameron, Ogg et al. 1967) did not show any real outcome differences between PD and HD, but there were never any strictly comparative trials, (Ahmad, Shen et al. 1985) and PD was plagued by a high complication rate (Vaamonde, Michael et al. 1975). The changes in demography and severity of ARF during this period was only shown in retrospective analyses (Turney, Marshall et al. 1990; Bellomo 2006) and there was, and still is, no realistic measure of the optimum 'dose' of dialysis required by acutes. More recently, a controlled study from Vietnam (Phu, Hien et al. 2002) showed that, compared to haemofiltration, PD had greater mortality, requirement for additional dialysis and, surprisingly, costs. These findings have significant implications for the management of ARF outside developed countries.

The perceived inadequacy of PD became an issue only from the 1980s (Nolph and Sorkin 1988), when its use declined with the advent of technological alternatives. Industrial development of dialysis monitors and membranes for the ESRD market greatly increased efficiency (as measured by solute clearance) allowing a marked reduction in the length of time needed for each dialysis session. This, together with plummeting item-costs for disposables and vast investment in chronic facilities, freed up machines and staff which could be deployed for ARF. Dialysis changed from a physician-provided procedure to one delivered by more numerous (and less costly) nurses and technicians, again having a significant impact on dialysis availability. The development of continuous dialysis systems, which shared with PD the advantage of a

[201] There were isolated pockets in which this general trend was less obvious. Particularly, at the LGI the HD facilities remained primarily committed to ARF (although PD was also used). That the focus on ARF was maintained was partly due to the continuing demand from the regional tertiary specialties within the hospital (trauma, cardiothoracic and neuro-surgery, intensive care, etc) and also because Parsons saw himself as a specialist in acute, not chronic, renal failure and had been instrumental in creating the chronic facility offsite at St James' Hospital, the ex-municipal Poor Law non-teaching hospital in Leeds.

‘gentle’ treatment less likely to cause cardiovascular instability but with the potential for greater flexibility, effectively condemned PD to history. Again, sophisticated machines, attractively packaged and promoted, have been enthusiastically adopted in preference to a simpler procedure, despite there having been no critical assessment of the relative merits of the different dialysis modalities.

7.3. Access to the circulation

The Achilles heel of haemodialysis has always been the simple but crucial question: how may blood be taken from and returned to the patient in sufficient quantities to render the machine efficiently adequate to its purpose? As the Leeds group demonstrated very early, the addition of a blood pump to the dialysis circuit greatly enhances the efficiency of the procedure, with considerable clinical and logistic benefit. However, a pump does not overcome the very real difficulties of accessing the circulation. These difficulties might include:

- ease, repeatability and safety of insertion of access device
- blood vessel damage
- impact on the patient: appearance, limitation of movement
- longevity of access device
- device materials (including biocompatibility) and cost
- additional requirements: nursing care, facilities for asepsis, anticoagulation
- potential complications: haemorrhage, infection, thrombosis/embolism, neurological or vascular injury.

The early history of vascular access has been given in a previous chapter, but in summary was as follows. Originally access was achieved by surgical cut-down to a peripheral artery and vein, the wrist or elbow being by far the main sites. A cannula, usually home made from glass, was inserted under direct vision and the vessel tied off. The operators used whatever materials were to hand, but these improved with time following the commercial availability of sterile sharp needles and plastic cannulas. Such equipment had been produced for general use, not specifically for dialysis. The blood vessels were destroyed by the procedure, which was perforce only single use. Long-term repeated dialysis was therefore precluded.

After unsuccessful attempts by others, including Alwall, Belding Scribner’s team in Seattle devised a semi-permanent access device (Quinton, Dillard et al. 1960). This shunt, announced in 1960, succeeded because of the availability of new materials such as

Teflon, developed outside the medical sphere but adaptable for clinical use. Although the Scribner shunt has been hailed as the harbinger of a new era in renal medicine, it was in practice extremely problematic, in large part because of the materials used. Chris Blagg brought two shunts back from Seattle on his return to Leeds in 1963, but these were found to be very disappointing in practice (Hopewell 2004). Nevertheless the device was widely taken up if only because it was better than the alternative. Leeds later modified the insertion technique and reported successful use of home-made shunts in 271 dialyses in 65 patients, of whom 28 had CRF (Clark and Parsons 1966).

Access for ESRD patients was revolutionised by the description of the surgically-created internal arteriovenous fistula (Brescia, Cimino et al. 1966), but this was of no use in the acute situation as it takes some weeks for the operation to heal and the fistula to mature. Before the use of fistulae became routine, Stanley Shaldon, then at the Royal Free Hospital, devised a technique for the cannulation of the femoral blood vessels to enable repeated dialysis (Shaldon, Chiandussi et al. 1961). Whilst this was superseded by other developments for chronic dialysis, it became the mainstay of access for acutes.

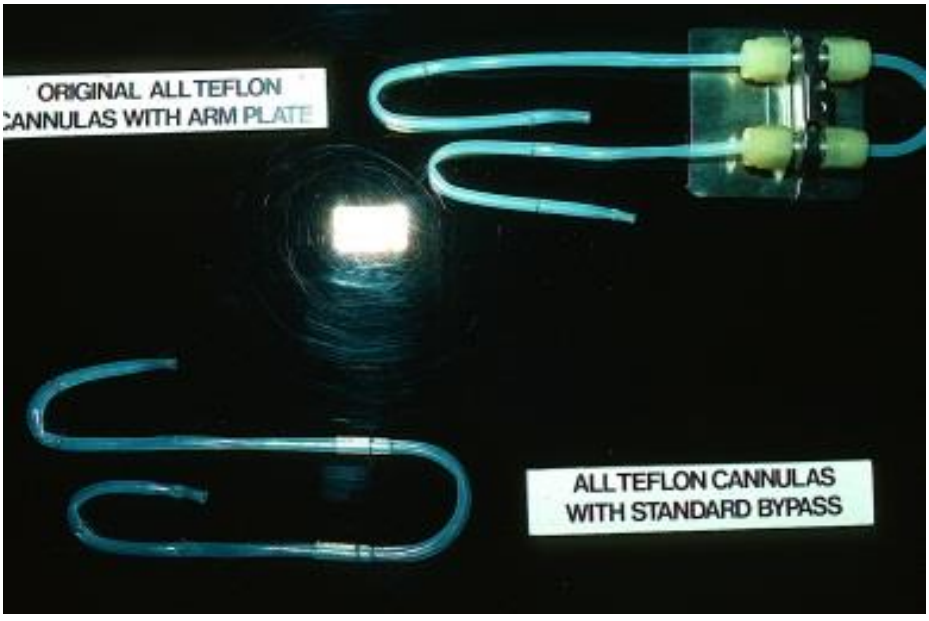

Fig 7.1. Early Scribner Shunts

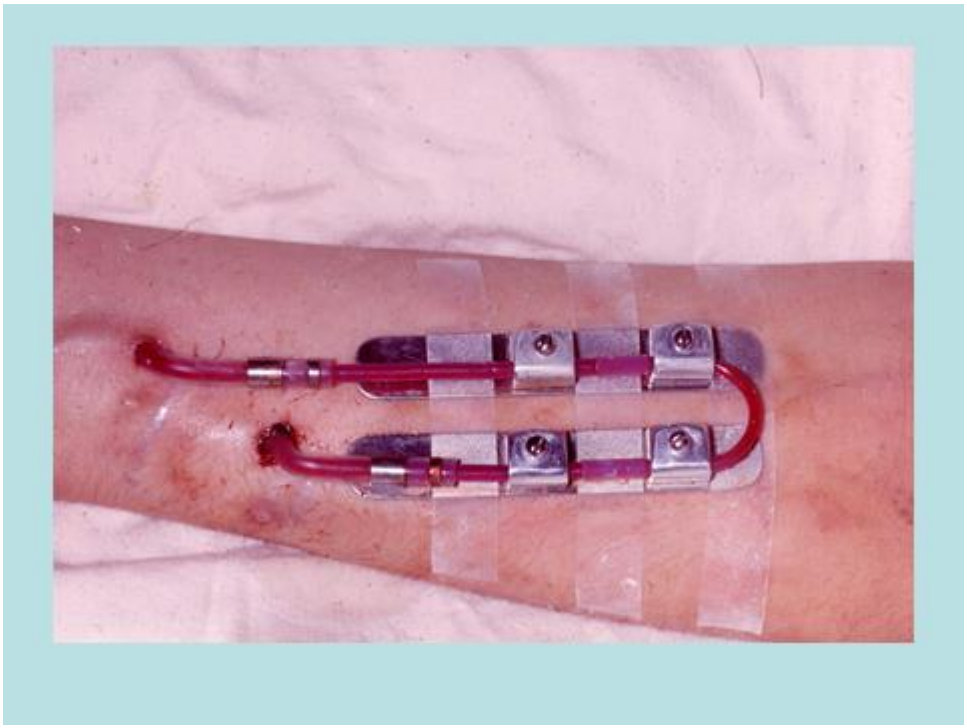

Fig 7.2. Early Scribner Shunt in Place

Fig 7.3. Shunt at End of Operative Procedure

The technique used by Shaldon, and developed by Robert Udall of Newcastle for use in subclavian and other vessels, was only possible because of developments in radiology. Then and now the Seldinger technique is used (Seldinger 1953): a suitable central vessel is punctured with a hollow needle, through which a flexible round-ended wire is introduced. This wire is used as a guide along which is passed a dilator of the puncture hole followed by a blunt floppy cannula of large internal diameter which can be left in place without risk of internal injury (Fig 7.4).

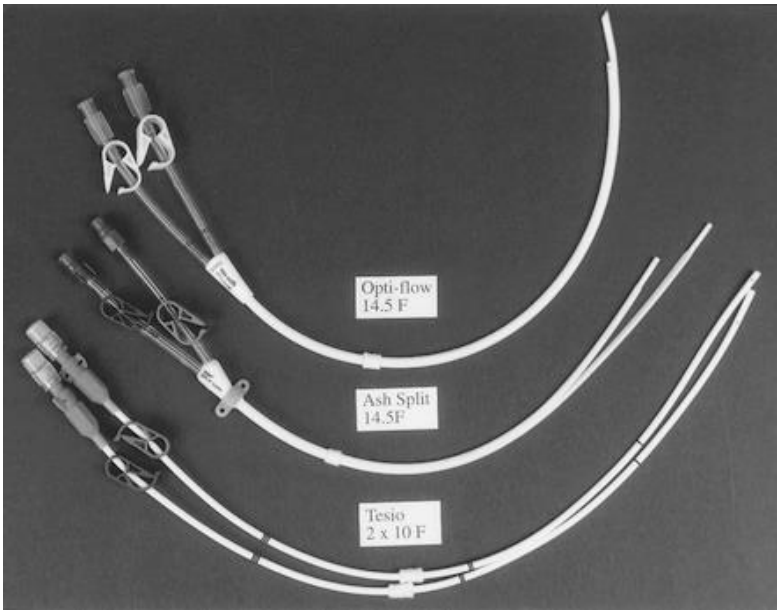

Fig 7.4. Examples of Indwelling Central Venous Cannulae

The Seldinger technique is routine in cardiology, radiology, long-term intravenous nutrition, cancer chemotherapy, etc. Consequently there is a large-scale market driving commercial production and refinement of the equipment. Renal medicine, specifically dialysis for ARF, tapped into this existing market. From at least 1980, all ARF patients have been dialysed via central lines, made of polyurethane or other complex plastics, inserted into the femoral, internal jugular or subclavian veins. The ability to create immediate, durable access to the circulation had two effects: vascular access effectively ceased to be a barrier to dialysis and central vein cannulation is particularly appropriate for continuous therapies in the ICU, thereby opening up an even wider potential range of patients for treatment.

7.4. New, adapted, and developed haemodialysis technologies

The demands of ESRD treatment through the 1960s and 1970s stimulated increasing commercial involvement in dialysis with a number of Swedish, French, German, Italian, Japanese and American companies committing significant resources to dialysis machines and disposables. At the same time it became acceptable for academic centres to look at clinical, technical and theoretical dialysis problems. It has already been noted that, from its inception, dialysis had been regarded by the scientific elite as unworthy of academic enquiry as it appeared to be little more than empirical engineering loosely based on scientific principles but not generating worthwhile intellectual challenges. Both the process and its clinical consequences were legitimated as subjects of academic interest by the rapid expansion of dialysis from the 1970s and also by directed programmatic

commercially-funded investigation. The market enabled manufacturers to reach a critical mass in which they were not only able to afford to support in-house and sponsored research, bu they were also required to do so to maintain a competitive 'edge'. Industry focused on machines, seeking competitive refinements in the capital market[202]. The application of electronic developments resulted in machines that became sophisticated computers for dialysis delivery and control. Developments in plastics technology produced membranes which not only cleared larger molecules but which were also consistent in structure, stronger and could be spun into any desired configuration (Pusineri and Paris 1988). The net result was the mass production of a range of highly efficient dialysers which were cheap and easy to handle. However, the large pore size meant that the membranes were 'leaky', potentially transferring dangerous volumes of water. This required improvements in the control mechanisms of the dialysis machines, the resultant sophistication of which allowed modifications of the dialysis technique such as haemofiltration. The market, because of the huge investment by governments in chronic dialysis, was sufficiently large to sustain the iterative relationships between industry and academic clinicians[203] and the introduction of membranes with new characteristics required adaptive development of machines.

An unintended consequence of the production of hollow-fibre capillary dialysers with 'leaky' synthetic membranes for the ESRD market was their application for the continuous treatment of ARF. Academic dialysis-related activity, although remaining only a small proportion of total nephrological research, focused on what might be called dialysis efficiency: the practical, clinical and theoretical considerations that determine the successful maintenance of life by renal replacement therapy. These research areas, together with commercial interests, kept returning to a central problem of dialysis: the artificial membrane mediating between the patient's blood and the dialysate. The centrality to dialysis technology of the evolution of the membrane will be considered in detail because of its eventual significance for ARF.

[202] "…the huge medicoindustrial complex that has grown up around clinical nephrology." Rennie, D. (1977). "Nephrology comes of age." N Engl J Med **297**: 1461-1462.

[203] The repeated appearance of the Seattle group led by a clinician (Scribner) and an engineer (Babb) in the early development of dialysis is noteworthy, usually in cooperation with commercial firms: 1965 piston pumps to mix dialysate concentrate with Milton Roy Corporation; 1967 similar but cheaper and more sophisticated machine with Drake Willock. Not until the early 1970s did a commercial firm (Cobe Laboratories, already in the dialysis field through blood line manufacture) produce a machine (combining all components) independently of academic clinician involvement.

7.4a Developing concepts in dialysis

The conceptual progress of dialysis technology may be summarised as follows. The dialyser membrane is the interface between the system and the patient's blood and is therefore the final determinant of the adequacy of the dialysis process. The performance of the membrane is affected by its structure and geometry, and its utility is governed by its strength, malleability and suitability for industrial production processes. Historically, cellulose from the packaging industry was available and was adopted for use as the semipermeable membrane and, slightly modified, remained in use for 40 or more years. But there were practical and theoretical difficulties: cellulose membranes are relatively fragile, not really amenable to any configuration other than sheets, and they allow transfer of only low molecular weight solutes and small volumes of fluid. In its most widely used format, the Kiil flat-plate dialyser, the dialyser had to be assembled by hand and the resulting artificial kidney was so large and heavy that it required a supporting stand. The staff costs and inconvenience were considerable. Further, it had long been known that the small molecules such as urea that accumulate so obviously in renal failure are relatively non-toxic and cannot explain the full syndrome of uraemia. HD with cellulosic membranes removes small molecules efficiently but patients, although not dead, remain chronically unwell. This lead to the 'middle-molecule hypothesis': that accumulation of various (largely unspecified) metabolites >1000 Daltons caused the symptoms of uraemia. Therefore, the academics argued, membranes with larger pores were required.

The accelerating expansion of long term dialysis from the 1960s not only demanded an increasing cohort of nephrologists to deliver this treatment, but also opened up a new field of academic endeavour: the study of the syndrome of chronic renal failure maintained by dialysis, that is to say the progression and continuation of the disease process which would previously have been curtailed by the death of the patient from biochemical imbalance (Peitzman 1992; Peitzman 2001). Part of the developing and funded interest was directed towards the treatment itself, usually following the pattern of seeking an explanation for accumulated clinical observations. Most research was, in this sense, reactive and the pace of this increased as new technologies were introduced (primarily by industry, but occasionally as a commercial response to academic concepts) bringing new clinical observations which could be studied.

It is worth reiterating that throughout the 1960s to the 1990s, technology-related attention was applied exclusively to the treatment of ESRD. New dialysis concepts and devices were transferred uncritically to the treatment of ARF, the acute patient being a co-beneficiary of the very much greater (numerical, financial, commercial) effort directed towards chronic treatment. There is no reason to suppose that treatment developed for the chronic situation was in any way inappropriate for ARF, but it was only very much later that a technology (continuous systems) was specifically applied to ARF. Theory and practice in dialysis were not sequential but occurred in parallel, each reacting to the other. It is simpler to consider concepts and technologies separately to try to understand the theory and, perhaps more importantly, the practice that were transferred to ARF with social and methodological consequences.

The application of long term dialysis unmasked a number of complications of the chronic uraemia syndrome which appeared not to be improved by the treatment. Included in these are anaemia, neuropathy, bone disease and other problems which became a burden to the patients whose lives had been prolonged by dialysis, which came to be perceived as not 'adequate'[204] to reverse all the features of chronic uraemia. The concept of adequacy originated with clinical observations by the Seattle group and others (Babb, Popovich et al. 1971; Teschan, Ginn et al. 1974; Babb, Strand et al. 1975) and rapidly became the subject of academic research into the mathematics and physics of dialysis performance (Shinaberger 2001), becoming increasingly complex as dialysis modalities, membranes and machines changed. Eventually some consensus arrived at a usable measure of dialysis performance in terms of biochemical measurement (which came to be accepted as a surrogate for adequacy because it was easier to measure and monitor than symptoms) which could be used to set standards and compare different treatment regimens. These numerical concepts were developed for ESRD patients on maintenance dialysis and transferred uncritically to the treatment of ARF, the assumption being that the numerical biochemical parameters were equally applicable, an assumption that has never been tested. Although adequacy has come to mean a

[204] The Oxford English Dictionary allows three meanings of 'adequate', of which two have been used without clear distinction to describe dialysis and its shortcomings: either 'fully sufficient, suitable, or fitting' or (in logic) 'fully answering to, or representing'. Thus dialysis may be considered to be adequate if it prevents death from uraemia, at one extreme, or if it is sufficient to restore (near-) normal health, at the other. It follows that 'adequacy' of dialysis has at times been used as an expression for the aspiration of optimal treatment, whilst at others it has meant the least quantity of dialysis commensurate with acceptable health (and financial) outcomes.

mathematical formula[205], improved dialysis performance so defined has been associated with an improvement in the debilitating complications experienced by patients, both acute and chronic, but cause and effect has never been proved. Despite the huge volume of work from the 1970s to the present, what is lacking is an understanding of the relationship, if any, between measurable metabolites and observable symptoms[206]. A practical solution to the methodological difficulties of measuring the efficiency of dialysis has been the use of the simplest clinically measurable formula (the urea reduction ratio) to standardise treatment, although it is well known that urea is itself relatively non-toxic. The justification for a usable formula to measure dialysis quantity was, in the end, the need to define the minimum essential ('adequate') treatment for long term dialysis patients[207]. The driving force for this was both the increasing demand for treatment and financial constraints[208]. The combination of more efficient technology and reduced funding[209] forced a reduction in treatment times, perhaps to the detriment of the patients, from 8 to 4 hours in the 1970s and down to as little as 2.5 hours in the 1980s. Simultaneously with these attempts at mathematical reductions of dialysis performance, the technology itself was changing. In particular, the physicochemical properties of the new membranes meant that not only was dialysance of small molecules performed efficiently, but they also had other effects not achievable with cellulosic membranes, such as clearance of large molecules. The mathematical modelling of urea clearance as a surrogate for efficiency or adequacy may inadvertently have been a measure of the removal by the dialyser of some more fundamental metabolites.

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[205] Cameron has argued that reliance on mathematical formulae has inhibited exploration of different conceptual and practical approaches to the treatment of uraemia: "..lack of any clear target as to what was to be achieved in chemical and engineering terms by the process of dialysis, in the continued absence of clear ideas what the uraemia syndrome was, or how it came about. Because targets were set using easily measurable parameters such as urea clearance, new developments tended simply to be extensions of old, rather than radically new approaches." (Cameron 2002, p245)

[206] "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." (Cameron 2002, p245)

[207] "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 accurate description of the quantity of dialysis was clearly evident." (Cameron 2002, p246)

[208] "…in many countries, especially the United States, organizational and financial constraints in units whose government funding per dialysis was decreasing steadily throughout two decades came to determine what dialysis patients received, not what they might need." (Cameron 2002, p234)

[209] The Medicare fee per dialysis session reduced from $138 in 1973 to $126 in 1992, despite inflation and a real increase in costs (Cameron 2002, p251, fn 30). In response, the predominantly for-profit dialysis facilities reduced the length of each dialysis session thereby increasing the throughput of patients, treating more patients/machine/day. It became clear that mortality among American ESRD patients was greater than in the UK, Europe or Japan. Outside the USA there was no commercial imperative to reduce dialysis times so drastically.

For acute patients, even more than for ESRD, there has never been an understanding of what actually causes morbidity and death when the kidneys fail, apart from fluid accumulation causing pulmonary oedema. Acutes are a non-homogenous group that challenges detailed physiological analysis. The limit of understanding is that, in the absence of timely spontaneous renal recovery, ARF is fatal and that when superimposed on other organ dysfunction, any degree of acute kidney malfunction significantly worsens prognosis. Apart from this, there is a general 'feeling' among clinicians that acute patients tolerate uraemia less well than chronics (but this may simply be a reflection of the speed of the changes). Faced with the obvious fact that the outcome in ARF remained poor, if not actually worsening, the only clinical option was to optimise the sole treatment. This desire, based largely on hope rather than evidence, not only lead to the rejection of PD but also to the uncritical adoption of criteria developed for ESRD, not necessarily reflecting pathophysiology but rather administrative convenience. The use of mathematical surrogates as measures of dialysis efficiency fuelled later controversies over the type and intensity of extracorporeal support required by critically ill patients.

It has been known from ancient times (Pelis 1997) that blood clots immediately on contact with an unnatural surface, and it is arguable that the invention of extracorporeal circuits became feasible only after the identification, isolation and commercial production of heparin[210] as an effective anticoagulant. However, this gross interaction between blood components and artificial surfaces is not what is meant by 'biocompatibility', a term that came into usage from the late 1970s to encompass the idea that contact with a surface might activate blood components (platelets, leucocytes, the complement cascade) which are then reinfused into the patient causing clinical effects. As will be seen, the problem of biocompatibility was inadvertently largely solved by the introduction of new polymer membranes, whose lack of interaction with blood was a serendipitous observation not a designed benefit. How a membrane may, or may not, stimulate blood components remains speculative, but the concept came to be used in debates on the optimum treatment of ARF. These debates became largely sterile following the empirical decision by most clinicians to switch from cellulose to synthetic

[210] The 'discovery' of heparin is a contentious story Marcum, J. A. (1997). "The development of heparin in Toronto." J Hist Med All Sci **52**: 310-337, Marcum, J. A. (2000). "The origin of the dispute over the discovery of heparin." J Hist Med All Sci **55**: 37-66. and its clinical application for dialysis was one of missed opportunities Fellner, S. K. and M. L. Purkerson (2002). "Gordon Murray: heparin, hemodialysis and hubris." Am J Nephrol **22**: 271-277..

polymer membranes, which just happen to be more compatible, a technological change actively promoted by industry.

7.4b Membranes

The physicochemical properties and chemical engineering of modern dialyser membranes is extremely complex (Klein 1998). Although the characteristics of polymers that would be essential for dialysis membranes had been predicted mathematically (Yasuda, Peterlin et al. 1969; Yasuda, Lamaze et al. 1971), most developments in dialysis during the 1970s and 80s came not from directed research but rather from empirical adoption (and occasional modification) of polymers developed for other purposes which, on testing, demonstrated properties suitable for use in dialysis. Previously, dialysis had been performed with regenerated cellulose membranes, essentially unchanged from those pirated from the packaging industry in the 1940s and it is arguable that, but for the commercial impact of ESRD treatment, there would have been little stimulus for membrane research and development. A German textile fibre manufacturer, Enka of Wuppertal (later Akzo Nobel Membrana), commenced large scale manufacture of cuprammonium cellulose (cuprophan) flat sheets in 1966. The impact on the firm's commercial status is illustrated by its turnover which rose from 1m DEM in 1966 to 54m DEM in 1976 (Vienken, Diamantoglou et al. 1999).

Entirely independently of dialysis applications, major chemical companies explored the development of polymers for use in reverse osmosis (RO) for water purification and for industrial ultrafiltration processes. At the same time, the companies producing these polymers for industrial and textile applications also developed techniques for spinning hollow fibres (advantageous for, among other things, allowing a large surface area within a compact overall size). Laboratory research, again largely commercial, began to analyse the microscopic structure of the polymer fibres and the way that this influenced their behaviour. It transpired that polymers found to have a potential for RO or ultrafiltration all had similar structures with asymmetrical geometry: inner and outer skins (later shown to control dialysance) and a core with voids or channels which conferred the hydraulic properties. The beginnings of the understanding of the properties of polymers in the 1970s coincided with the postulation of the 'middle molecule' hypothesis, which although never proven provided a stimulus for the search for dialysis membranes with greater solute clearances.

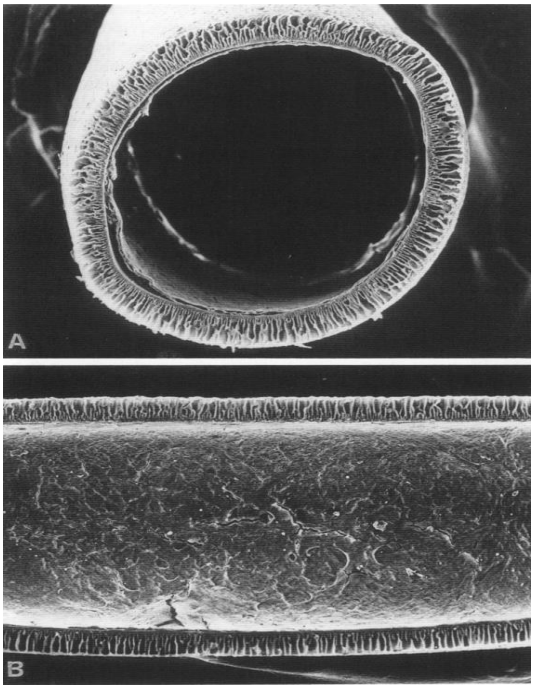

Fig 7.5. Scanning Electron Micrograph of Synthetic Polymer Hollow Fibre

The origins of modern dialysis membranes can be traced to the Dow Chemical Co. which patented an extruded hydrolysed cellulose acetate hollow fibre in 1960, initially for RO but reconfigured for dialysis in 1964 and which underwent clinical trials in 1968. The introduction of hollow fibre (capillary) dialysers was somewhat fortuitous (van Stone 1997). For reasons which are not clear, the American Army sponsored a long-term research programme on blood oxygenators which appears to have started during World War II. An experiment with a hollow fibre blood oxygenator failed, but the device worked as an artificial kidney (Stewart, Baretta et al. 1966). Hollow fibre dialysers, after much development and refinement, came to totally dominate the market. Also in 1968, the Chemstrand Division of Monsanto developed a technique for making hollow fibres from acrylic copolymers, a production process still in use. These fibres were intended for industrial and textile use, but the Monsanto asymmetric polyacrilonitrile (PAN) fibres were later developed by French and Japanese companies into very successful high-flux dialysers. One of the earliest, and most successful, examples of a 'designed' membrane was the AN69 developed by Rhone-Poulenc of France. This was a co-polymer of acrylonitrile and methallyl sulfonate, the latter being incorporated because of its negatively charged ionisable groups. This was originally deemed to be a desirable feature as in some ways this mimics the kidney's glomerular basement membrane (Cheung and Leypoldt 1997). Also in 1968, the Aerojet Corporation produced a cellulose acetate membrane copolymerised with diethylaminoethyl cellulose. The

intention had been to provide heparin-binding sites on the membrane to minimise anticoagulant use in dialysis, and hence the risk of systemic bleeding. In 1981, after the concept of biocompatibility had been formulated, it was found that this Hemaphan membrane, unlike other cellulose derivatives, did not activate complement. It was some time later that academic work showed that small quantities of copolymers formed domains on the membrane surface and that these somehow interfere with the formation of the total complement attack complex. The recognition of the subtle surface effects of domains of copolymers (such as polymer alloys containing small quantities of polyvinylpyrrolidine in polysulphone or PAN) had a significant impact on the understanding of membrane characteristics and resulted in the deliberate search for similar effects[211]. By the 1980s, the dialysis market was sufficiently robust to sustain specific research and development.

"[P]rogress in the 1970s relied more on mechanical developments and industrial reduction to practice than in improvements in membranes" (Klein 1998, p260). A programme of research had been initiated by the Artificial Kidney Chronic Uremia Program (AKCUP) of the NIH, founded in 1965. The development of dialysers was possibly a unique example of collaboration between academia, government and industry (Burchardi 1998), the singular feature of AKCUP being that rather than limiting grants to educational establishments, the NIH programme managers were also permitted to contract with commercial firms. A direct result was collaboration between Amicon Corporation and the University of Pennsylvania which produced a haemofilter (Silverstein, Ford et al. 1974) made from an acrylonitrile and vinyl chloride copolymer (originally intended for making flame retardant fibres) and using basic technology developed for RO. This innovative product had little hydraulic resistance, allowing high flux or ultrafiltration of fluid, but its structure impeded dialysis of solutes. This was but one of the many problems the new technology threw up which required further technological changes to solve. In this instance, large chemical companies had by the end of the 1970s shown the feasibility of organic solvent casing of polymers, which could then be tested for the effects on dialysance.

The clinical utility of the vinyl polymers developed in the 1960s was limited by their inability to maintain their structure when exposed to steam, necessitating gas or radiation

[211] "…some interesting coincidences…led to some new approaches to improve biocompatibility…" (Klein 1998, p262)

sterilisation, each of which carried its own problems[212]. Consequently, attention in the 1970s was directed towards stiffer engineering plastics with higher glass transition temperatures. Of these, bis-phenolA polymers proved the most suitable and the majority of membranes subsequently in clinical usage are derived from these. The first of the new generation to be tested (by Amicon in 1973) proved to be the most successful. Polysulphone was originally used as a flat sheet support for interfacially formed RO membranes and for industrial ultrafilters. These glassy bis-phenol polyesters also had high ultrafiltration coefficients but poor dialytic clearance. Thus, until the late 1970s, synthetic membranes could only be clinically useful if used in series with a cellulosic dialyser, so that fluid ultrafiltration and solute dialysis were performed sequentially. This created problems with the available dialysis machines which required technical solutions which will be discussed later.

The inadequate dialytic performance of synthetic membranes was revolutionised in 1977 when Fresenius (who were already heavily involved in dialysis) acquired the patent for polymer alloys copolymerised with polyvinylpyrrolidine (PVP). Initially developed by a commercial research laboratory to alter the membrane structure of engineering plastics, the addition of small quantities of PVP resulted in a homogenous cross sections of the core of these stiff polymers resulting in improved wettability and enabling thin-walled hollow fibres to be produced (Klein 1998). This, together with organic solvent casing, resulted in compact dialysers with high hollow fibre density and good hydraulic and dialysis performance. From the mid-1980s these were widely adopted for clinical use, becoming the exclusive type of dialyser from the 1990s.

Dialysis membranes, the interface between patients and their treatment, have always been made from available adaptable materials: from cellophane packaging to complex polymers created initially for industrial processes. Academic research had thrown up the desirability of new membrane characteristics, but developments were driven by industry (including its own R & D) encouraged by an expanding and lucrative market. Although commercial interests dominated technological progress, budget constraints in the healthcare market modulated this by restricting widespread adoption of technical developments until the costs were reduced precipitously.

[212] Dialysers sterilised with ethylene oxide gas had to be carefully and thoroughly flushed with large volumes of saline before they could be safely used.

7.4c Development of dialysis machines from c1965

Until at least the early 1960s, dialysis was potentially dangerous for the patient because the machines incorporated no safety or control features, these being considered to be unnecessary as each dialysis session was supervised by a physician who, at least in theory, could recognise and intervene in any untoward events[213]. Quality was entirely subjective and even reduced to assessing the state of the dialysate by taste and smell.

Increasing numbers of chronic patients meant that this personalised treatment was no longer feasible, except perhaps for the most critically ill patients. Of necessity, there was an increasing trend to incorporate safety devices into the machines through the 1960s (Cameron 2002, pp196-197), a move encouraged by the delegation of the dialysis procedure to nurses, technicians and even to patients themselves, perhaps in their own homes. These early dialysis 'monitors' blended dialysis fluid from salts and water, measured the quality and temperature of the fluid, and detected air in the circuit (to avoid air embolism). In about 1963, Charles Mion of Montpellier, working at Seattle, showed that acetate could be used as a buffer (Mion, Hegstrom et al. 1964), which avoided the problem of precipitation of calcium within the dialysate. This allowed the creation of integrated dialysis systems for individual patient use such as first produced by the Sweden Freezer Company and the Drake-Willock Corporation, examples of cooperative developments between industry and academic renal centres. (It was later found that the quantity of acetate administered during dialysis exceeded the patient's metabolic capacity, resulting in acidosis and cardiovascular instability. Again it was Scribner's multidisciplinary group in Seattle (Graefe, Milutinovich et al. 1978) who devised a solution: reverting to bicarbonate, but modifying the mixing of dialysate by the machine. Once the technical problems had been solved by manufacturers, bicarbonate became the standard.)

Dialysis monitors became increasingly sophisticated until the 1980s, incorporating computerised safety and control features (the first microprocessor-controlled machine was introduced by Gambro in 1977), but remained essentially unchanged in their basic principles. That was until the introduction of high flux synthetic membranes, the wider

[213] "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." Cameron 2002, p196

uptake of which during the 1980s demanding the incorporation of new control mechanisms and a rethink on the quality of water used in dialysis (monitors use about 600mls/minute of water to produce dialysate). The appearance, in the 1970s, of a severe progressive dementia and fracturing bone disease, eventually shown to be due to aluminium toxicity, in long term dialysis patients (Alfrey, LeGendre et al. 1976) alerted the renal community that even potable mains water contained potentially harmful material. The solution was the production of ultrapure water by sequential filtration, deionisation, reverse osmosis, and salt exchange softeners.

None of the foregoing was directly relevant to the treatment of ARF. Water preparation plants became large (room-sized) and therefore appropriate only for dedicated renal units where they could serve several machines simultaneously. Many ARF patients require treatment away from the purpose-built renal facilities, for example in ICUs. The options for these patients were limited because it proved unfeasible to provide ultrapure water at every possible site of activity. Either small RO units must be provided or an optimistic assumption made that short-term exposure to contaminants would not harm the acute patient too much. This could be considered to be a further example of ARF ceding priority to ESRD in technical and clinical thinking about dialysis. What was of concern for ARF was the development of synthetic high flux membranes, which could potentially transfer bacterial endotoxins from contaminated dialysate, not a problem with less porous cellulose membranes. This also heightened the need for the production of sterile water for dialysis.

Of more immediate practical significance was the convective mass transfer of fluid across these membranes which, if not controlled, could have disastrous effects on the patient. Various technical fixes to control the transfer of water were tried by manufacturers through the1970s because without precise fluid control the synthetic membranes were unusable in practice. Initially (1971) Rhone Poulenc tried fixed volume tanks in the machine they developed for use with their AN69 membrane. Later, Fresenius used reciprocating pistons but it was not until 1989 that various turbine flow meter-governed devices, now the standard, appeared on the market from different manufacturers. The combination of precise programmable fluid removal with the clearance characteristics of the polymer membranes remains the apogee of dialytic treatment, applicable equally to ARF and CRF. The technological developments designed to cope with the hydraulic characteristics of synthetic polymers were later utilised in the treatment of ARF. Precise management of fluid efflux and inflow was a

sine qua non for the design of continuous dialysis systems, which are absolutely dependent on programmable and measurable fluid control. The adaptation of fluid control and of polymer membranes are the prime examples of the transfer of technology, developed to address the problems of ESRD, to the treatment of ARF.

7.4d Continuous therapies

As suggested earlier, the development of dialysers for haemodiafiltration is possibly a unique example of collaboration between academia, government and industry (Burchardi 1998). Commercial interest in the need to develop modifications of the machines to cope with the new synthetic high-flux membranes was stimulated by the NIH Contractors Conference in 1977 and a NIH-sponsored multicentre trial of haemodiafiltration in the

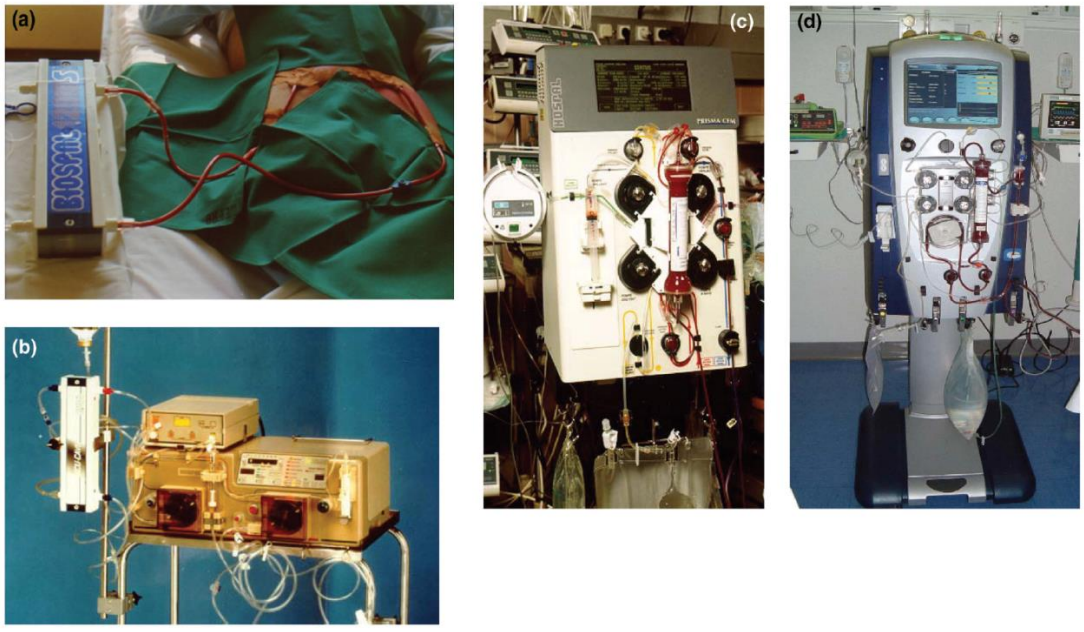

Fig 7.7. Evolution of Continuous Dialysis Therapies

a. Spontaneous CAVH. b. CVVH c.1990. c. Integrated CVVH/D c.1995 d. Advanced CVVH/D c.2010

USA and Germany[214]. This apparently connected and directed programme of research took an unexpected turn when a high-flux Amicon diafilter was connected, allegedly accidentally[215], to a femoral artery catheter and it was observed that the difference

[214] The National Cooperative Dialysis Study produced equivocal results with no clear clinical benefits from increased removal of 'middle molecules' Lowrie, E. G., N. M. Laird, et al. (1981). "The effect of hemodialysis prescription on patient morbidity." N Engl J Med **305**: 1176-1181..

[215] This story, although firmly embedded in nephrological folklore, bears little scrutiny. The technique for the insertion of a Seldinger catheter into the femoral vein precludes inadvertent arterial puncture. Even if this had occurred, the catheters would have been connected to a dialysis machine, which would have prevented blood flow (because of the occlusive roller pumps in the circuit) and the spontaneous ultrafiltration through the dialyser membrane would not have been observed.

between arterial and venous pressures spontaneously produced a significant filtrate. Initially thought to be useful only for the correction of fluid overload (Kramer, Kaufhold et al. 1980), this simple concept became known as continuous arteriovenous haemofiltration (CAVH) and was rapidly adopted for use in ARF in the intensive care unit (Dodd, Turney et al. 1982; Kramer, Schrader et al. 1982), receiving FDA approval in 1982 (Eisenhauer 1985). CAVH must rank as one of the most rapidly and widely adopted medical innovations. It was a new procedure that challenged established practice by providing renal replacement without the involvement of any obvious machine, with the negative connotations that machinery carries. Its attractiveness derived from its conceptual and mechanical simplicity, apparent safety and the immediate off-the-shelf availability of all the components.

Although newer materials and equipment facilitated the introduction of continuous therapy, it was not an entirely new concept. In 1959 Scribner's group in Seattle modified a large Sears-Roebuck deep freeze as a dialysate reservoir to allow continuous pumpless dialysis using a low-resistance Skeggs-Leonard dialyser (Scribner, Caner et al. 1960). The ingenious effectiveness of the arrangement was enhanced by the use of refrigeration which inhibited bacterial contamination. Glucose and salts in dialysate provide an ideal culture medium, which proved a major problem for long-term dialysis units until individual proportionating pumps were developed (again, a practical concept arising in Seattle). This solution to a perceived need for increased dialysis in ARF allowed continuous treatment for up to seven days (Murray, Hegstrom et al. 1961). Elimination of the blood pump was an important feature which greatly reduced the need for supervision (Scribner 1990) and was instrumental in reducing pressure on staff when Seattle commenced long-term dialysis for ESRD. The early patients were treated with 24 hours continuous dialysis once a week until it was realised that this was inadequate to control the complications of chronic uraemia.

The new technique was simple and cheap and its great advantage over conventional HD was that it did not destabilise the patient's blood pressure. CAVH owed its simplicity to having no moving parts (consisting as it did of just two plastic tubes and a filter with a drainage bag attached), but because it was dependent solely on the patient's blood pressure the solute clearance and fluid removal proved unpredictably inadequate if the blood pressure fell, a frequent occurrence in intensive care. Advocates of CAVH were wont to liken the device to the renal glomerulus in that it simply filtered plasma water and its metabolites in a quasi-physiological fashion. The analogy fell down

because the normal healthy glomerular filtrate is in excess of 100 ml/minute and CAVH was unlikely to achieve 20 ml/minute, equivalent to significant renal failure. The inadequacy of the system was a particular problem in the severely catabolic ARF patient, and there was an ever-present risk of dangerous arterial line disconnection. These considerations stimulated the search for various technical solutions, the net result being the invention of pumped continuous venovenous haemofiltration (CVVH)[216] (Forni and Hilton 1997). Although these developments occurred largely in academic centres, it required the involvement of industry (for example, Hospal in France, who also made filters from their AN69 membrane) before usable safe machines were available. In 1984/5 it was suggested (Ronco 1985) that the efficiency of CVVH could be enhanced by combining convective haemofiltration with diffusive haemodialysis. This required very sophisticated modification of equipment, only achievable by large commercial companies.

CAVH	Continuous arteriovenous haemofiltration
CVVH	Continuous venovenous (pumped) haemofiltration/ haemodialysis/ haemodiafiltration
Haemofiltration	Convective mass transfer of water and solutes across a semipermeable membrane, the rate of transfer being determined by the transmembrane pressure and the pore size. The amount of solutes removed ('clearance') is determined by the volume of blood-water crossing the membrane
Haemodialysis	Diffusive transfer of solutes (± water) across a semipermeable membrane between blood and dialysate. The clearance is determined by membrane characteristics, rate and direction of flow of blood and dialysate, and transmembrane pressure.
Haemodiafiltration	Combined dialysis and filtration

Table 7.1. Dialysis Methods

[216] The ad hoc devices constructed by various renal centres were ingenious but inadequate, being particularly suspect with regards to safety. It is improbable that any would be acceptable under current EU law. For example, the author, together with the Medical Physics department at the LGI, constructed a serviceable CVVH circuit by cannibalising HD machines and using 20 year old pumps found in a store. Although the device performed adequately, the later acquisition of commercial machines was a great relief to all users.

Fig 7.6. Patient undergoing extracorporeal circulation in ICU.

An initially simple procedure, based on the concept of attempting to mimic the natural function of the kidneys by continuous gentle removal of fluid and solutes, became complex. Modern CVVH machines are a sophisticated computerised collection of pumps, controlling the infusion and removal of large volumes of fluid. The machines are programmable and, because of the inbuilt complex safety devices, can be left to run continuously, the attendant nurse having to occasionally change fluid bags and note the figures from the computer read out, activities which are easily assimilated into normal ICU nursing practices. In many respects CVVH has become just another of the many machines utilised in ICU, so many that often the patient is the least visible item in each bed-space (Fig 7.6).

7.5. Contested interpretations and applications of technology

Limited use of dialysis for ARF was accepted somewhat grudgingly during the 1950s, an acceptance pushed initially by enthusiastic medical sponsors. Medical opinion was also ambivalent about the introduction of widespread dialysis for ESRD in the 1960s, the enthusiasm again limited to specialists but, more significantly, also endorsed by the public. Thereafter, the benefit of dialysis was unquestioned, despite its obvious difficulties and costs. It was vigorously promoted by a swelling specialty, who

positioned themselves as patient advocates whilst simultaneously promoting their own interests.

General acceptance of HD as the treatment for renal failure progressively changed the question presented for nephrological debate from *whether* to dialyse to *how* to dialyse and then to *who* should be dialysed and by *whom*. This debate was informed by the available technology, directed clinical research, and social factors mainly relating to the establishment of specialty power structures. A recurrent theme in earlier writings was that dialysis was frequently applied too late in the course of the illness when the moribund patient had accumulated complications such as internal bleeding, muscle wasting or sepsis which made their survival at best doubtful. Delay in the application of dialysis was multifactorial: late referral, shortage of staff and facilities, over-long dependence on conservative treatment, and lack of understanding not only of the natural history of the disease but also of the role and effects of the technology. The problem and possible solutions were identified by the Leeds group (Parsons, Hobson et al. 1961) and others (Salisbury 1958) early in the dissemination of dialysis, but this work was never acknowledged by advocates of the intensification of dialysis. Small observational studies (O'Brien, Baxter et al. 1959; Easterling and Forland 1964), including the one coining the phrase 'prophylactic dialysis'[217] (Teschan, Baxter et al. 1960), showed improved survival if dialysis was initiated before patients became too uraemic. Based on the hypothesis that uraemia is the cause of complications, most (Kleinknecht, Jungers et al. 1971; Kleinknecht, Jungers et al. 1972; Kleinknecht and Ganeval 1973) but not all (Fischer, Griffen et al. 1966) felt that the improved patient survival was due to a reduction in complications.

The momentum for the introduction of 'prophylactic' dialysis appears to have come from a meeting held in October 1957 under the auspices of the Surgeon General at the US Army Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas (Teschan 1989; Teschan 1998). Teschan recollects that the motivation for the meeting was the death of a patient from sepsis, cachexia and would dehiscence, an outcome contrasting with the optimistic results in the contemporary literature. One suspects that he also had an additional agenda: to cement official support for dialysis-related research.

[217] The phrase 'prophylactic' dialysis enjoyed prolonged popularity, but it is difficult to know the meaning of the adjective. Presumably, the intended message was that earlier and more intense dialysis was a measure used to prevent, or as a precaution against (OED), such complications of ARF as bleeding, sepsis, muscle wasting, and poor wound healing (and death?).

Although he later claimed to have assembled "all those who had published on acute renal failure by that date", the attendance list[218] is not comprehensive. While several big names (such as Kolff, Merrill, and Schreiner) attended, there were only two non-Americans: Gabriel Richet (one of several figures at two Paris centres) and Graham Bull (whose views on dialysis were well known). Surprising omissions included Frank Parsons, who certainly had published by then. The participants pooled the case records of 1044 patients, showing an overall mortality of 49% (66% after trauma). Following the meeting, the Surgeon General authorised Teschan to investigate various aspects of dialysis technology, including a study of the MacNeill-Collins $1m^2$ dialyser (developed by the military) for 'prophylaxis'.

These investigations coincided with improved vascular access devices and the introduction of the Kolff-designed Travenol twin-coil machine, both of which made the procedure of dialysis more approachable. Not only was the technology easier to use, more efficient, and machines and disposables readily commercially available, but there was also a marked expansion in trained and experienced staff. Additionally, the procedure was increasingly delegated to the more numerous nursing and technical staff[219]. Simultaneously, dialysis centres were increasing in number and capacity, and it is noteworthy that the earliest papers on prophylactic dialysis came from a US Army base treating, in peacetime, a small number of civilians with ARF and so having spare capacity. Thus circumstances gradually allowed nephrologists to move from just trying to cope with demand to a position in which there was space to develop the procedure, predicated on the belief that if dialysis was good, then more of it would be better. Despite later studies (Gillum, Dixon et al. 1986) and reviews (Conger 1995; Karsou, Jaber et al. 2000) casting some doubt on the benefit of increased dialysis intensity, this idea never went away. Earlier studies compared patients with extremes of blood biochemistry, but later work compared standard 'adequate' dialysis with very intensive treatment, showing no differences in outcome (VA/NIH Acute Renal Failure Trial

[218] Attendees at 1957 Study Group on Acute Renal Failure: Bill Bluemle, Graham Bull (London), Hadley Conn, Paul Doolan, Garland Herndon, John Kiley, Willem Kolff, Arthur Mason, John Merrill, Milton Rabini, Gabriel Richet (Paris), George Schreiner, Paul Teschan.

[219] It is not clear when it became apparent that an MD degree was not a necessary prerequisite for performing dialysis. Photographs of early dialysis, for example in Korea and Leeds (*Your Life in Their Hands*, BBC, 8/4/1958) show 2 – 4 doctors preparing and conducting dialysis, the scene being redolent of a surgical operating theatre. Almost certainly, the use of nurses as deliverers of dialysis was forced by the workload demands of ESRD patients, but perhaps also doctors became bored with a procedure that had become routine rather than innovative and challenging.

Network 2008). Nevertheless, it became accepted practice that dialysis should be initiated well before uraemic symptoms occur, and the dose (frequency and efficiency) of dialysis (Silva, Pomeroy et al. 1964) must be sufficient to maintain each patient in reasonable biochemical and fluid control. This, of course, became progressively easier to achieve as equipment became more sophisticated.

Some consternation and considerable reflection on the policy of 'more is better' was provoked by a speculative but influential paper (Conger 1990) that posited the iconoclastic theory that haemodialysis actually impedes renal recovery from ARF. The hypothesis was based on the demonstration of fresh areas of acute tubular necrosis on biopsy or at post mortem (Solez, Morel-Maroger et al. 1979) which appeared to be temporally related to episodes of hypotension, some of which may have been related to dialysis sessions. Additionally, animal models show impaired autoregulation of renal blood flow during ARF, thereby conceivably making the kidney more vulnerable to changes in blood pressure. Although the suggestion may be speculative (and unprovable in the clinical setting), it did provide a possible explanation for the observation that the time taken before the kidneys recovered independent function (and the completeness of this recovery) appeared worse than that reported in the 1950s and 1960s. That the nephrologists' treatment for ARF may be at least partially harmful stimulated the search for alternative equipment (membranes) and techniques (CVVH), a search encouraged by the commercial availability of alternatives. There is, however, little evidence that well-conducted HD causes cardiovascular instability (Schortgen, Soubrier et al. 2000; Vinsonneau, Camus et al. 2006) sufficient to be treatment-limiting. Notwithstanding the lack of hard evidence of their relevance, the time to recovery or the development of further renal injury (such as converting from non-oliguric to oliguric ARF) became surrogate markers of the safety of the dialysis procedure, most particularly in studies of 'biocompatible' membranes (Hakim, Wingaard et al. 1994; Schiffl, Sitter et al. 1995; Himmelfarb, Tolkoff Rubin et al. 1998). As the significance of these clinical end-points is based entirely on a theoretical adverse effect, it is perhaps not surprising that larger studies (Jorres, Gahl et al. 1999; Romao, Abensur et al. 1999; Gastaldello, Melot et al. 2000; Schiffl 2006; VA/NIH Acute Renal Failure Trial Network 2008) or reviews (Jacobs 1997; Karsou, Jaber et al. 2000) could not demonstrate clear benefit from different dialysis materials or methods.

Further injury to the failing kidneys could also theoretically be caused by blood components activated during passage through the extracorporeal circuit. Additionally, or alternatively, contact with the artificial surface might render the cellular or humoral components of the immune system in some way deficient, making the patient more vulnerable to infectious complications. These ideas, arising from academic laboratories, fitted neatly with the perceived advantages of synthetic biocompatible membranes and together prompted clinical trials, most of which were commercially sponsored. As with other clinical studies in the field of dialysis, the first published studies, all involving small numbers of patients, showed significant outcome benefits from biocompatible membranes (Hakim, Tolkoff-Rubin et al. 1994; Schiffl, Lang et al. 1994; Schiffl, Sitter et al. 1995; Himmelfarb, Tolkoff Rubin et al. 1998; Schiffl, Lang et al. 1998). Although these studies can be criticised on methodological grounds (Turney 1994; Jacobs 1997; Vanholder and Lameire 1999)[220] they did raise the intriguing possibility that the dialysis procedure, by provoking an inflammatory response, could evoke further kidney injury and systemic complications, which together may increase dialysis-dependence and/or mortality. This, together with the convenience, plummeting costs (about 80% reduction) and active marketing, meant that the use of cellulose membranes effectively ceased, to be replaced by biocompatible alternatives. That later studies, all methodologically superior, failed to show any clear benefits or differences in cellular responses with synthetic membranes (Kranzlin, Reuss et al. 1996; Jorres, Gahl et al. 1999; Romao, Abensur et al. 1999; Gastaldello, Melot et al. 2000; Jaber, Cendoroglo et al. 2000) did nothing to reverse this trend. Synthetic membranes in capillary format became standard, and industry ceased to offer cellulosic membranes and other configurations. Technological and commercial expediency effectively settled the biological debate by removing the possible comparators.

[220] It is difficult to assess the standing of the much-cited publications from Munich, the scientific integrity of one of which having been questioned following review by the host institution (Drazen, J. M., J. R. Ingelfinger, et al. (2003). "Expression of concern: Schiffle H, et al. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 2002; 346: 305-10." N Engl J Med **348**: 2137, ibid.. In a series of papers, Schiffl reported significant benefits for clinical outcomes with use of biocompatible membranes and high-intensity dialysis, but there is a suspicion that these studies are repeated analyses of an accumulating series of patients. Significantly, the paper with the most patients reported that the mode or duration of dialysis does not influence renal recovery Schiffl, H. (2006). "Renal recovery from acute tubular necrosis requiring renal replacement therapy: a prospective study in critically ill patients." Nephrol Dial Transplant **21**: 1248-1252..

Once continuous therapies had been accepted as an alternative to intermittent HD, at least in the ICU, proponents repeated the pattern of argument by proposing that earlier institution and greater intensity of treatment improved outcomes (Druml 1996; Druml 1996; Ronco, Bellomo et al. 2000). A large volume of literature, from a limited number of authors, strongly promoted prompt use of high-volume CVVH, positing that aggressive biochemical control would inevitably lead to improved results without the potential problems of HD. Again clinical research had been directed to the quest for a benefit from technical or procedural changes. However, the assumption that any benefit might exist or be demonstrable was itself based on a series of unproven assumptions. ARF had come to be defined by measurable disturbances of routine biochemical analysis: a raised serum creatinine equals ARF. But a diagnosis reliant on biochemistry alone does not convey the significance traditionally attributed to diagnosis, that of individual prognosis. The retrospective statistical analysis of the degree of chemical perturbation in groups may give an indication of risk but not of definite individual outcome, and the concept of risk is generally misunderstood. These and other suppositions lead to a circular, and potentially self-defeating, hypothesis that as ARF has been chosen to equate to biochemistry, then biochemistry is both the measure of the severity of the illness and the measure of efficacy of treatment and hence the ultimate determinant of outcome. Early studies did indeed appear to show benefit, but all were methodologically deficient (Jakob, Frey et al. 1996; Kierdorf and Sieberth 1996; Kanagasundaram and Paganini 1999). Larger randomised studies failed to demonstrate any advantage of CVVH over HD (Mehta, McDonald et al. 2001; Uehlinger, Jakob et al. 2005; Vinsonneau, Camus et al. 2006; VA/NIH Acute Renal Failure Trial Network 2008), or of intensity of CVVH (Bouman, Oudemans van Straaten et al. 2002), or of early application of CVVH (Bauer, Marzi et al. 2001; Bouman, Oudemans van Straaten et al. 2002), or of CVVH for non-renal indications (Cole, Bellomo et al. 2002; Hoste, Vanholder et al. 2002). Inconsistencies in the definition of ARF and clinical heterogeneity further invalidated many trials.

A statistical stratagem (meta-analysis) has been increasingly used to combine and compare clinical trials which may otherwise be contradictory, under-powered or in some other way deficient. Trials of different dialysis modalities are consistently methodologically inadequate. None fulfil the criteria for randomised controlled clinical trials (RCCTs). For a variety of reasons, not least of which is the lack of uniformity of

ARF patients, it is highly unlikely that it would ever be possible to conduct a trial of all dialysis-related variables that would be both methodologically acceptable and also give a clear-cut answer. Consequently, it has been fashionable to undertake meta-analyses of treatment in ARF. Unfortunately, these synthetic analyses have frequently given discordant results (Teehan, Liangos et al. 2003). Thus one meta-analysis showed a significant survival advantage conferred by synthetic biocompatible membranes (Subramanian, Venkataraman et al. 2002), whereas another demonstrated no benefit (Jaber, Lau et al. 2002). The former analysis had included an additional observational study which, because of its size, distorted the results. Even then, the survival disadvantage appeared confined to unsubstituted cellulose (cuprophane) membranes, which had ceased to be commercially available before the meta-analysis had been published. Similar anomalous results have also been obtained by meta-analyses of continuous dialysis therapies. One, after considerable statistical manipulation, showed benefit from continuous v. intermittent dialysis (Kellum, Angus et al. 2002), but concluded that there was in fact insufficient data to reach a conclusion. Conversely, an equally well conducted analysis (Tonelli, Manns et al. 2002) could find no difference in survival or renal recovery whatever type of dialysis was employed. The statistical anomalies arise in large part from the necessary inclusion of nonrandomised trials in any analysis. There is an 8 – 20% variance in the estimation of the magnitude of treatment effects between randomised and nonrandomised clinical trials (Ioannidis, Haidich et al. 2001), which results in uninterpretable distortions when observational and other methodologically suspect studies are incorporated into statistical analyses. Yet, without such studies there could be no analysis of treatment of renal failure.

The foregoing might appear to be a digression, but is in fact the prelude to a critical question: where does this leave the practitioner? The espousal of "evidence-based medicine" is absolutely contingent on there being sound evidence. If the evidence is equivocal, the practitioner is justified in continuing to choose whatever treatment 'feels' best or is simply available: that variability perhaps being determined by institutional or commercial policies. Advocates of a particular therapy can reasonably select whatever 'evidence' supports their conviction, as has stereotypically been the case in debates between intensivists and nephrologists over renal replacement therapy.

It could further be argued that all trials of technological or pharmaceutical interventions in ARF will inevitably fail to show consistent clinical benefit because they

are predicated on the naïve assumption that the (partial) correction of even important aspects such as the blood biochemistry might materially influence the outcome of such a complex syndrome as ARF. As an example, a retrospective comparison showed that the death rate in patients receiving CVVH was twice as high as those on HD (Swartz, Messana et al. 1999), but review of the data showed that the excess mortality was entirely due to co-morbidity, i.e. not directly related to ARF. The cause of death during ARF is multifactorial, the risk depending on factors related to the patient, the precipitating and coexistent diseases, acquired complications, and treatment (Woodrow and Turney 1992). Of these, the patients and their co-morbidity may be the most important (Stott, Cameron et al. 1972; Butkus 1983; Conger 1988). As the causes of death are legion, mortality may not be an appropriate end-point for studies of technology (Bell and Smithies 1996). Similarly, complications of acute uraemia may respond better to interventions other than dialysis: for example, pharmacological control of gastric acidity has had the greatest impact on the prevention of gastrointestinal haemorrhage, a frequent and often fatal consequence of uraemia (Woodrow and Turney 1992). The argument that improved outcomes of ARF will result from attention to all aspects of care (Turney 1994) has been endorsed by a review of published evidence (Jakob, Frey et al. 1996) that, irrespective of the technology employed, the quality of overall care determines outcome.

7.6. Social contestations of new technology

The rapid assimilation of CVVH into routine ICU practice triggered a number of complex debates, both social and medical. Although physicians continue to write treatment prescriptions, all forms of dialysis machines are sufficiently self contained as to require little professional intervention. Renal replacement therapy is no longer a laborious and tiresome procedure demanding of expertise and staff time. The procedure has been delegated through the medical hierarchy; it is routine, not exciting or challenging or intellectually stimulating and therefore less interesting to physicians and less demanding of their skills. This social change has been largely uncontentious, although in many jurisdictions there are continuing issues around the ‘extended role of the nurse’. The other social change precipitated by the introduction of CVVH has been the often acrimonious and still unresolved competition for ownership of the procedure

between nephrologists and intensivists[221]. This turf war has particular intensity in those health care systems where procedures equate to remuneration and where collaborative health care delivery by professional equals may be, and often is, financially penalised. In salaried services, shared care depends on the *modus operandi* of individuals and institutions[222]. Intensivists argue that as CVVH is now part of the standard armamentarium of the ICU, it is simply part of the whole management package, along with mechanical ventilation and other organ support devices. Further, CVVH might have a role in non-renal critical care situations such as sepsis. Nephrologists, on the other hand, have tended to take a superior attitude, arguing that the total management of ARF is a physicianly activity requiring expertise beyond just the application of mechanical devices. Further, survivors of ICU will require on-going medical care and renal support.

Both camps use the medical literature to promote their viewpoints, usually through editorials or opinion pieces. A flavour of this contested area, which applies solely to continuous renal therapies in the ICU, may be gleaned from the literature. A policy statement by the American College of Physicians (Committee 1988) defined the skills required for the administration of continuous therapies: "…the cognitive skills require in-depth knowledge of nephrology and the overall management of patients with acute renal failure…" (p900) "…because the procedure is easy to do, there may be a tendency for physicians less familiar with the overall management and diagnostic assessment of renal disease to use it." (p901)

This document is important because the ACP stated that compliance was required for the granting or maintenance of privileges (whether or not this had an effect on the behaviour of physicians or institutions is not known). Membership of the policy committee was notably exclusively nephrological. It is therefore not surprising that the required skills could only be acquired from a formal renal training programme. This positional statement was reiterated by an NIH conference (largely of nephrologists) which stated that:

> "The indications for renal replacement therapy in ARF…must be individualized by nephrological consultation."

[221] "…ICUs are increasingly a focal point for tension between medical specialists."Charytan, C., A. A. Kaplan, et al. (2001). "Role of the nephrologist in the intensive care unit." Amer J Kid Dis **38**: 426-429.

[222] The author enjoyed a professionally fulfilling, but demanding, role in a huge (by British standards) ICU complex in which the input of all specialists was coordinated by the intensivists, to the apparent benefit of all, but especially the patients.

The positioning by nephrologists for ownership of the new technology, a predominantly but not exclusively American exercise, continues unabated. The intensivists' position is that CVVH should be controlled by them largely because it is continuous (Bellomo, Cole et al. 1997). The claim that 'closed' ICUs, as in Australia where intensivists have exclusive access, results in better outcomes is unprovable. Nephrologists argue (Charytan, Kaplan et al. 2001) that their training, with broad skills in general medicine, makes them best placed as the primary physician for hospital patients with renal failure. The published debates have become quite vituperative:

> "…not incorporating the physician with the most profound knowledge base of the system would be an important compromise in patient care...Continuous renal replacement therapy is a nephrological technique which must remain under the team leadership management of nephrology." (Paganini 1996)

> "…the difficulties inherent in treating patients with MOF [multiorgan failure] are so great that they should not be compounded by the introduction of avoidable problems that reflect nonclinical issues – the structure and funding of services, or worse still, the size of the various medical egos involved. There is no room in the modern ICU for the prima donna or the dilettante." (Bihari 1996)

As with most debates, both sides have merits. On balance it would appear that intensivists have shown largely uncritical acceptance of CVVH because of its perceived practical advantages[223], theoretical benefits (for example, on mediators of the sepsis syndrome) and because ownership of the technique provided further confirmation of a definable existence and identity of the specialty. Nephrologists, on the other hand, developed the procedure of CVVH, although control of the technology passed to industry who marketed it directly to ICUs. Renal physicians then attempted to define the indications, effects and comparative worth (versus HD, an established procedure controlled by nephrologists) of the technology. Throughout, nephrologists took a more critical 'scientific' approach to continuous therapies: whether this was intellectual rigour or merely defence of the *status quo* remains an open question.

[223] One practical advantage of CVVH is precise fluid balance control. The attractiveness of this meshed with the one-time dogmatic commitment to 'optimising' cardiopulmonary measurements in the ICU, although the dependence on pulmonary artery catheters and indiscriminate use of inotropic drugs has lately been questioned.

In many respects, this was a sterile argument. Even by the early 1990s, the majority of British hospitals without on-site renal services were providing CVVH in the ICU (Stevens and Rainford 1992), the argument having been pragmatically decided by the utility and availability of the technology. It seems to be the case that, in many places, intensivists simply chose to ignore the controls, caveats and restrictions proposed by the official pronouncements of their nephrological competitors.

What remains both surprising and disappointing is the level of ignorance about the procedure. Most medical staff are unaware of the huge expense and potential futility of treating ARF in the ICU (Korkeila, Ruokonen et al. 2000) and certainly do not recognise that CVVH, despite its apparent simplicity, is significantly more costly than HD (Moreno, Heyka et al. 1996; Hoyt 1997), being 2-4 times more expensive than intermittent haemodialysis in the ICU (Manns, Doig et al. 2003). A final, worrying thought is provided by a survey (Ricci, Ronco et al. 2006) which showed that CVVH was used by 90% of the multinational multispecialty respondents, but 60% of intensivists and 40% of nephrologists were uncertain about how to prescribe and measure the 'dose' of CVVH. This raises serious questions about the general use of complex medical technologies. Attractive packaging and forceful marketing encourage purchase, but hard-to-comprehend technology obscures the actual purpose of the machine, which may come to be regarded as a self-contained self-managing 'black box' not requiring detailed human intervention.

7.7. Summary

The schematic representation of the changes in dialysis technology c.1965 – c.1995 (Fig 7.7) misleadingly suggests that development were sequential, precipitated by changes in other technologies. There was in fact overlap and contemporaneity. Some innovations were delayed for technical reasons, others because of marketing decisions, and yet others through a lack of immediate appreciation of their utility or simply because of cost. Some innovations had a brief commercial lifespan, being superseded by competing technologies.

Nevertheless a conceptual pathway can be constructed: scientific questions and clinical difficulties sought practical solutions, often achieved by adaptation of outside materials to solve specific dialysis-related challenges. The proposed solutions, at least in their unrefined form, often posed new complexities requiring, in their turn, further modification of equipment and practice. At the same time, technology in its broadest sense was changing: programmable control by microprocessors, polymers and other

materials became available for a variety of purposes. All of these developments were enabled by the large and profitable market created by the huge worldwide demand for long-term dialysis for ESRD. Major medical supply companies were encouraged to enter the market and to fund research and development, most obviously after 1972 when government-funded dialysis began to become available in the USA.

Concepts, technologies and practices developed for ESRD patients were uncritically applied to the treatment of ARF. Current theories on the science of dialysis and available technologies were transferred to ARF, in part because they seemed 'right' in the absence of evidence to the contrary and in part because there was no reasonable alternative that might be more applicable to ARF. Peritoneal dialysis had been largely rejected as inadequate for ARF, although it was acknowledged that it had some attractions, including the fact that as a slow gentle treatment it was less likely to further upset the unstable critically ill patient. It was, however, in those very patients that PD was least effective in controlling the biochemical disarray that had been agreed to be the measure of kidney failure and the adequacy of its treatment.

Even in retrospect it is difficult to determine to what degree the eventual technology adopted specifically for ARF was the result of compromise between programmatic research and the merely fortunate concurrence of materials and circumstances. Membranes developed to address potential problems of long-term dialysis for ESRD also proved suitable for use in continuous therapy for ARF, which combined the physiological advantages of PD with the clearance of toxins achieved by HD. Although dialysers composed of these polymer membranes can work without a mechanical extracorporeal circuit, they were found to be more effective when combined with a machine-driven control and delivery system. Such machines required modification of devices originally developed for intermittent dialysis for ESRD. These refinements were produced by an industry already committed to renal therapy. It would appear that commerce identified the potential for continuous therapies before they were widely adopted by the profession. That is to say, the profession was offered an attractive treatment already at an advanced stage of development, which it enthusiastically adopted. Clinical investigation of this treatment then followed, seeking an acceptable scientific rationale for its use.

The significance of continuous therapy in late-20th century medicine lay not in its technical sophistication but in the fact that it seemed to be entirely appropriate for a changing pattern of ARF. By that time, the majority of patients suffered acute renal

dysfunction in the context of multiple system failure in the ICU. The character and demography of ARF had changed as medical practice had changed in the last quarter of

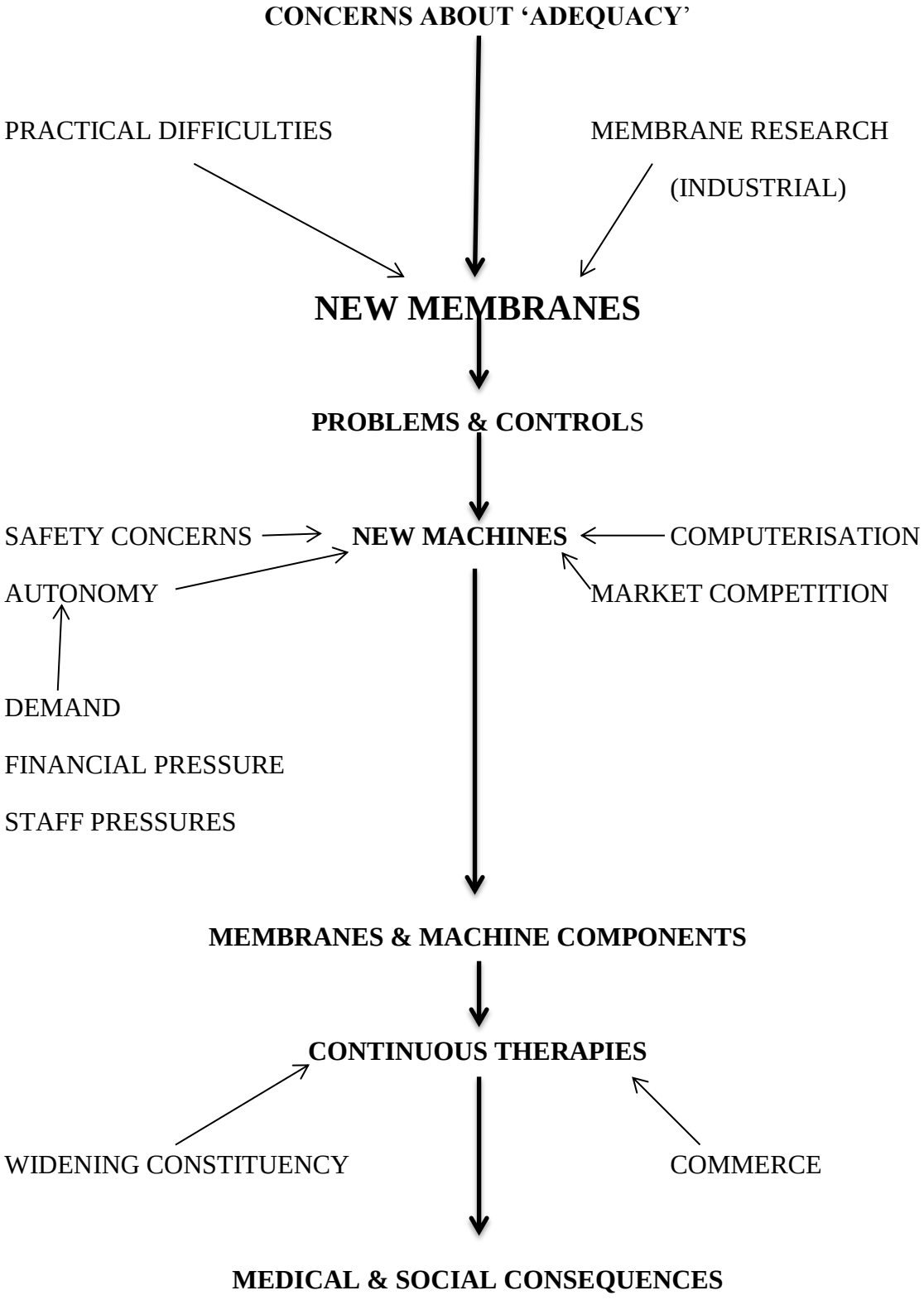

Fig 7.7. Schematic Representation of Dialysis Development

the 20th century. ARF became the diagnostic emblem of borderline survivability. The new technology seemed to be well matched to the new patient constituency in a different setting, a consequence of which was that it could now be applied to even those *in extremis* who would previously have been judged to be untreatable.

The social consequences of the new technology were not limited to debates on the futility and seemliness of aggressive medical intervention. Autonomous machines appear to require no specialist to manage them: at one level they merely serve a function among a plethora of life-supporting machines. The question then arises as to who should own and govern the device: the specialist defined by dialysis and renal dysfunction or the specialist claiming ownership of the whole critically ill patient.

8. LATER ACUTE RENAL FAILURE.

8.1 Introduction

ARF is a symptom resulting from a concatenation of clinical events impinging on an individual patient to produce an abrupt reduction in kidney function. This manifestation is thus defined by the effect on and the response by the patient as well as the medical situation precipitating it. A truism recognised by today's practitioners is that ARF is not the same as it was half a century before: disease and demography have changed, modifying and modified by the technological and therapeutic response. From about 1990, the term Acute Kidney Injury (AKI) became increasingly substituted for ARF, a tacit acknowledgement that the condition had changed. To an extent, however, this was a conceit, an attempt to widen the definition to increase its presence in the medical lexicon and to heighten the influence of the nephrologists and intensivists who claimed ownership of renal dysfunction and its technology.

In chapter 2, the reification of ARF was described in terms of an iterative process involving patients, circumstances, medical practice and attitudes, technology and resources. Consensus on the definition of ARF was eventually reached and there was more or less agreement about the optimal available treatment: haemodialysis. However, none of the condition, patients or technology remained static, the changes being gradually assimilated into medical thought, which facilitated changes in practice and behaviours. From something of a medical curiosity with a marginal technology, ARF emerged as iconic of late 20th century medicine in as much as the condition was largely shaped by changing technical factors. Moreover, the inconstancy of this symptomatic condition arose not from within and of itself but in response to changes in the socioeconomic status of populations, in other diseases and most prominently in changing medical practice.

This chapter seeks to map these changes, based on data from the Leeds series placed in an international and time-dependent context. Definable categories will be used to illustrate facets of change, with the ambition of deriving the generalisable from the specific. Discussion of causes and consequences seeks to establish a case for ARF being semeiotic of late 20th century medicine, for it can be regarded as a symptom defined by medical, social and technological factors.

The shifting of the paradigm of ARF is extraordinarily complex and has challenged medical opinion and practice for 30 years or more. Although there is consensus (Bellomo 2006) that things are not what they used to be, analysis of what has actually changed is difficult, depending as it does on epidemiology, demography, redefinition of clinical categories, refinement of technology, and perhaps subtle but significant changes that are yet to become apparent[224]. In essence, the problem as aired towards the end of the 20th century had two aspects: the incidence of ARF appeared to have risen and to continue to rise, creating a significant medical and financial burden; despite increasing effort and investment in treatment, the outcome appeared not to have proportionately improved and indeed to have actually worsened. Although there may perhaps be an aura of self-justification in some of the published apologies for this train of events[225], there doubtless is a difference between ARF now and then.

8.2 Recognising change.

In 1972, Stewart Cameron and colleagues from Guy's Hospital asked a question which continues to reverberate throughout the nephrological community: why the persistently high mortality in ARF? (Stott, Cameron et al. 1972) The positivist attitude prevalent throughout high-tech medicine would naturally have led to the assumption that accumulation of technological development and refinement, and of practitioner knowledge and expertise, would inevitably build on and improve the initial success of dialysis. After all, surely the modern sophisticates could achieve more than did the neophytes with their primitive machines in the 1950s. The figures simply did not support this optimistic deterministic assumption: fewer patients were surviving ARF than had a decade earlier. The proposed explanation was that patients and their disease were changing, and that this change had largely passed unnoticed. The unstated inference was that ARF was no longer a discrete entity but had become, in the majority of cases, merely one facet of an increasingly complex clinical situation (which later acquired the acronym MOSF: multiple organ system failure). The logic of the new thinking could lead to the conclusion that dialysis should no longer be given primacy in the

[224] The situation is further bedevilled by the absence of consistent definitions throughout the enormous literature. There was some improvement in later publications following general acceptance of severity scoring systems in ICUs, but this coincided with the move to redefine ARF 'downwards' to include less severe degrees of renal injury.

[225] Bellomo (2006, p560): "It is likely that the 50-60% crude mortality will remain unchanged…as it represents the level of performance acceptable to the healthcare system rather than a true reflection of its performance. In other words, as therapeutic capability improves and the system continues to accept a mortality of 50% as reasonable for these very sick patients, the healthcare system will progressively admit and treat sicker and sicker patients with ARF."

management of these patients: a direct threat to a specialty which had built itself around its totemic machine and the disorder in part defined by that machine. There has, however, been little or no debate about or investigation of this challenging conclusion.

Support for the hypothesis slowly accumulated (Butkus 1983) and was confirmed by the publication (Turney, Marshall et al. 1990) of more than three decades' experience of severe (dialysis-dependent) ARF at Leeds. This very long and very large series (Cameron 1990) showed:

- changing epidemiology (Figure 8.1), with the virtual disappearance of ARF resulting from obstetrics and trauma, which had been replaced by complex medical and surgical cases;
- a significant increase in the age of the patients from a median of 41y in the 1950s to 61y in the 1980s (Figure 8.2);
- a significantly reduced survival with increasing age (Figure 8.3);
- improved survival for males (and all patients if obstetrics were excluded) from the 1950s to the 1980s.

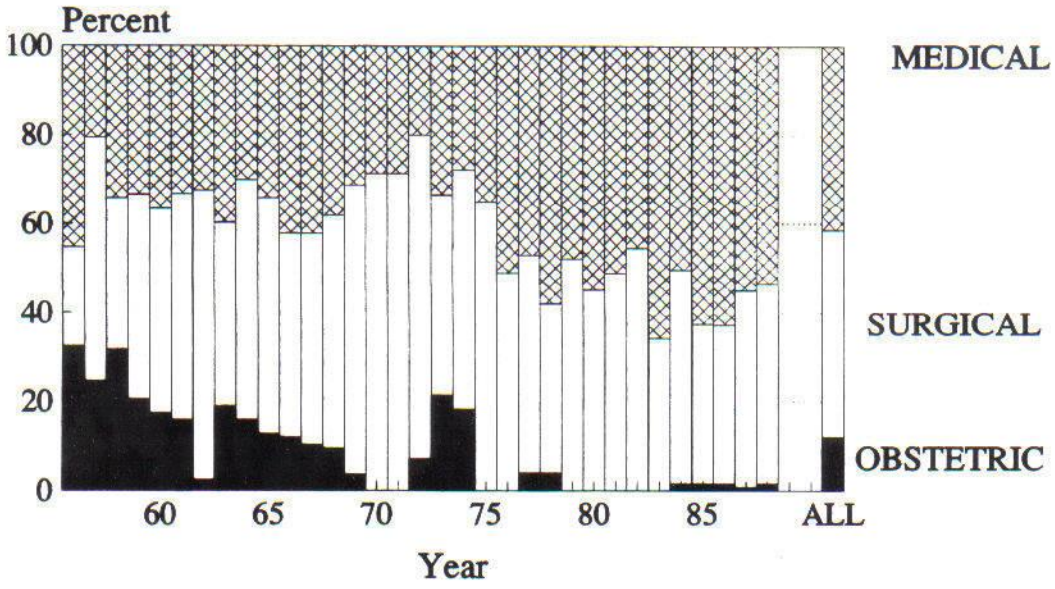

Figure 8.1. Frequency (%) of major diagnostic groups of ARF at Leeds

These findings have been corroborated many times (Druml 1996; Elasy and Anderson 1996; Ympa, Sakr et al. 2005; Lameire, Van Biesen et al. 2006), but require further excavation and contextualisation of the demography and epidemiology: how many and which people are afflicted by ARF, what are the causes and consequences of their problem, and has any of this changed in the 50 years of renal support?

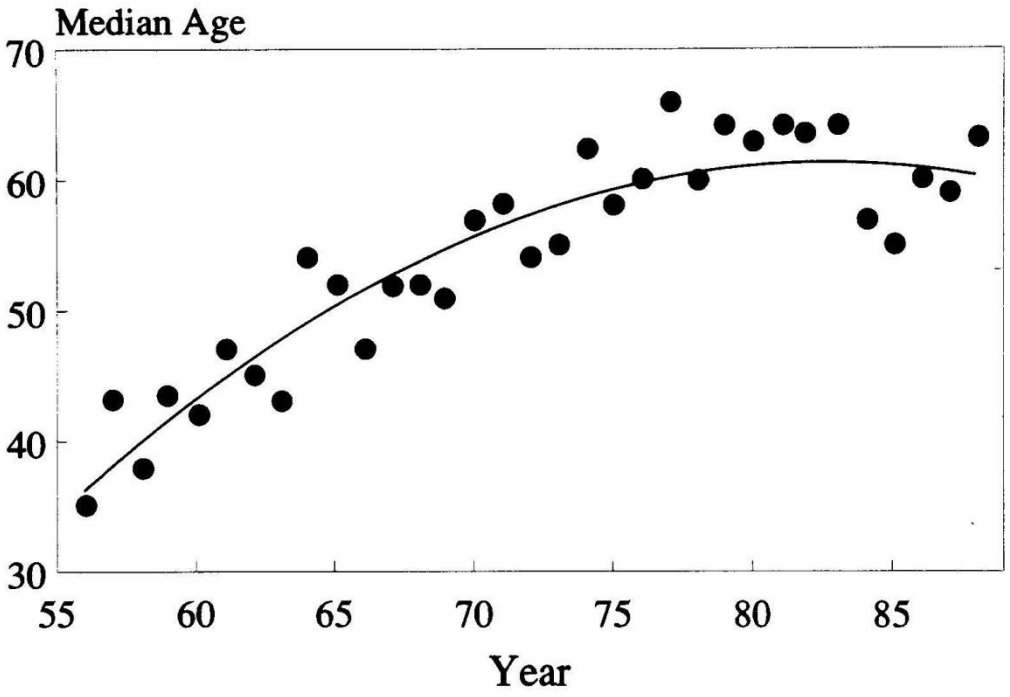

Figure 8.2. Age of Leeds patients 1956 - 1988

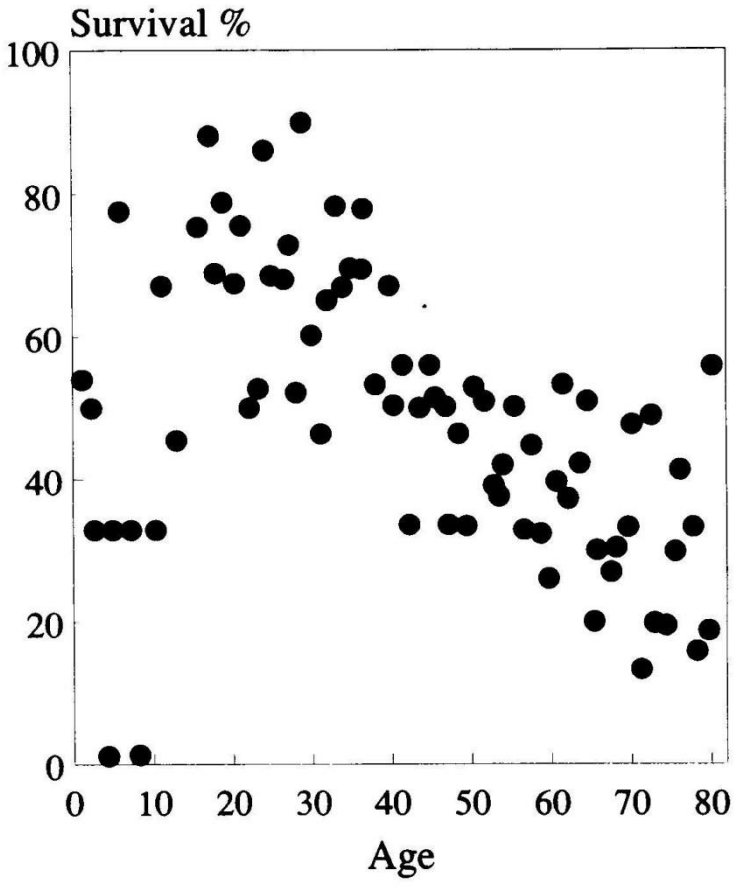

Figure 8.3. Mortality (%) with age, Leeds.

8.3 Demography

8.3a Age

The striking feature of recent patients in industrialised countries is that they are significantly older than those from the 1950s and 1960s or those from developing countries. In this respect, and in the distribution of the causes of ARF, developing countries in the 1980s and 1990s came to closely resemble Europe and the USA 30 or 40 years previously. There is evidence that a price for urbanisation and industrialisation is the acquisition of a westernised pattern of health: an ageing population with its associated burden of chronic disease. That ARF has become a complication of such disorders and an indicator of the human cost of treatment is supported by the gradual convergence of the demography and epidemiology of ARF between rapidly emerging economies such as India (Chugh, Sakhuja et al. 1989) and the West.

Population-based surveys of the incidence of ARF (variously defined) show without doubt that ARF occurs more commonly in the elderly. Thus in Devon (Feest, Round et al. 1993), the incidence progressively rose from 17.1/million/year in the population aged less than 50years to 623.6/m/y in those aged >80y (excluding prostatic obstruction)[226]. A comparable study in Scotland (Khan, Catto et al. 1997), using a lower threshold for the diagnosis of ARF, showed an exponential rise in the incidence of ARF with increasing age. Similar results have been obtained from Manchester (Hegarty, Middleton et al. 2005). The elderly have come to be disproportionately represented among ARF patients worldwide. For example, in Paris (Akposso, Hertig et al. 2000) only 4% of their patients were aged over 80y in the 1970s, rising to 40% in the 1990s. In Madrid (Pascual, Liano et al. 1995) the over 70s comprise 7% of the general population and 10.5% of all hospitals admissions, but 36% of the ARF patients. In Leeds (Rodgers, Staniland et al. 1990), 14% of the dialysed ARF patients in the 1960s were aged over 65y, rising to 32% in the 1980s. A similar preponderance of elderly patients is now seen in severe sepsis (Angus, Linde-Zwirble et al. 2001) and respiratory failure (Ely, Wheeler et al. 2002), both of which are not unrelated to ARF in the ICU. The shift in the age distribution has

[226] Incidence of ARF (per million population per year) in Devon and Scotland.

AGE	Feest 1993	Khan 1997
16-49	17.1	157
50-59	82.7	834
60-69	148.9	
70-79	485.9	2694
>80y	623.6	5188

been multifactorial: fewer young people developing ARF, because of changing epidemiology and improved first-line treatment, and the disappearance of any age-related selection for treatment. It is also indicative of the 'greying' of the population and, by implication, the associated burden of neoplastic, cardiovascular and other degenerative diseases which all increase in prevalence with advancing age. Again, ARF could be represented as a marker of a changing social and medical environment.

Does the simple fact of increasing representation of older patients solely determine the overall outcome? Do the elderly suffer from different medical problems, and are they more likely to die than younger persons? Ageing is associated with structural changes in the kidneys which reduce their functional reserve and render them more vulnerable to acute dysfunction. Additionally, the elderly undoubtedly have more concomitant disease, an indication of which is the observation that they consume twice as many medications as all other age groups combined. Many such drugs (such as those widely used for cardiovascular problems) carry a potential risk of causing or enabling ARF. Most studies appear to agree that age is an independent risk factor for both the development of ARF and subsequent death (Pascual, Liano et al. 1995; Lameire, Van Biesen et al. 2006), but this certainty becomes less clear if such studies are analysed in detail. For example, analyses at different periods all show that the very elderly have a remarkably good prognosis in ARF, with or without ICU care. In large part this is due to considerable selection of patients with little co-morbidity, in whom the outlook is much better than for the unselected patient population aged between, say, 60 and 79 years (Oliveira and Winearls 1984; Abreo, Moorthy et al. 1986; Dahlberg and Schaper 1989; Lameire, Verspeelt et al. 1991; Druml, Lax et al. 1994; Nierman, Schechter et al. 2001; Hsu, McCullough et al. 2007). In a large unselected community-based survey, age did not affect outcome (Feest, Round et al. 1993). However, as soon as the elderly start to develop complications, their mortality rises sharply. The elderly have little physiological reserve with which to combat accumulating medical complexities.

A confounding factor in the understanding of the effect of age is whether it has been considered to be a continuous variable or whether some arbitrary age (60, 65, 70, 80 years) has been chosen as the start of 'old'. The Leeds series showed that mortality progressively increased from age 41y, i.e. the 'elderly' pattern starts at a comparatively young age. This is to an extent supported by some evidence that peak mortality occurs in those aged c50 – c79 years (Feest, Round et al. 1993), even in the absence of an age-related selection bias. But of course what actually happens is that the pattern of disease

changes. The balance of evidence is that age *per se* is at most a minor risk factor (Wu, Rubin et al. 1990; MacEwen, Naik et al. 2011), but what is important is that age is a marker of severity of disease and co-morbidity (Groeneveld, Tran et al. 1991; van den Noortgate, Vogelaers et al. 1999; van den Noortgate, Mouton et al. 2003) and that older people are more vulnerable to superadded complications (Kass, Castriotta et al. 1992). The conclusion must be that severity of illness is the overwhelming factor determining outcome and that the association between rising age and rising mortality is a reflection of the heavier burden of disease in the elderly. That more older people have been treated for ARF or in the ICU in recent years reflects the greater proportion in the general population together with, and probably more significantly, declining negative age-based selection for invasive interventions indicating changed expectancy among recipients of health care, irrespective of age.

The increasing proportion of the elderly being diagnosed and treated for ARF in the last 20 years of the 20th century doubtless contributed to the observed worldwide increase in incidence of ARF (Lameire, Van Biesen et al. 2006). Earlier publications tended to include only those with severe renal dysfunction, equivalent to requiring dialysis. The tendency to expand the definition of ARF to include lesser degrees (by biochemical parameters) of renal injury inevitably resulted in an apparent increase in incidence. However, by using standard definitions from the enormous Federal diagnosis-related databases, there is clear evidence that ARF increased by 11-13% per annum between the late 1980s and the mid-2000s (Xue, Daniels et al. 2006), with a concomitant increase in those receiving dialysis. There are an estimated 115,000 patients each year being dialysed for ARF in the USA, of whom more than half die (Kellum 2002). Underlying or associated conditions, such as severe sepsis, also increased by similar amounts over the same time-frame (Angus, Linde-Zwirble et al. 2001; Martin, Mannino et al. 2003).

The rise in numbers of hospitalised patients with severe life-threatening problems such as sepsis or respiratory +/- renal failure has been consistent across all westernised countries. The proffered reasons for this increase do not appear to provide a full explanation. Certainly the proportion of elderly people is steadily increasing, but this is largely because the entire population is healthier, better nourished and less impoverished. Certainly, more invasive medical interventions were performed in more vulnerable patients. Yet the overall results of, say, cardiac surgery progressively improved during the last two decades of the 20th century. Many major operations have

been replaced by less traumatic radiological techniques: examples include coronary artery angioplasty, cardiac valve replacement, and abdominal aortic aneurysms. Improved radiological and serological investigations have meant that many disorders could be diagnosed at an earlier stage, thereby improving outcomes without radical surgery or other treatments. Within ICUs, potentially nephrotoxic agents such as starch-based colloids were abandoned on safety grounds (Brunkhorst, Engel et al. 2008; Wiedermann, Dunzendorfer et al. 2010). Pharmaceutical companies directed effort towards the development of safer chemotherapeutic agents which have replaced older highly toxic drugs, such as mitomycin C, which included ARF among their frequent side-effects. The purpose of this diversion is to raise caveats to challenge the general assumption that the consistently rising incidence of critical illness was the corollary of more adventurous intervention in serious disorders in an ageing population. Undoubtedly this narrative is applicable to the changes in medical practice in the 1960s, 70s and 80s but, I suggest, may not entirely account for the observed events thereafter.

The population of the westernised world progressively aged during the second half of the 20th century. Both as an absolute number and as a percentage of the whole, the proportion of older (>65 years) and very old (>80y) increased. In 1950 some 8 – 10% of the UK and USA population were aged over 65, with about 1% older than 80y. By the year 2000, 15.7% of the UK population and 12.6% in the USA were older than 65y and about 3.5% in their 80s or above. Figures for the demand on medical services from this ageing population are scanty, but between 2000 and 2010 the NHS saw a 48% increase in in-patient hospital stays for the over-65s and a 66% increase in the over-80s. This infers that the demand for medical care accumulates disproportionately with increasing age: the burden of ill-health rises exponentially with the linear increase in age.

Relating these demographic changes to the specific example of ARF encourages the following assumptions, which can be only partially statistically corroborated:

- withholding of advanced medical support (ICU, dialysis, etc.) became less age-determined with the passage of time;
- causes of severe acute disease in young adults became less frequent, for example from improved maternal health;
- new, aggressive interventions were progressively applied to older and older patients;
- chronic disorders increase in prevalence in the old, thereby exacerbating any acute illness.

If ARF uniformly visited all age-groups and if access to technological medicine was unfettered by any overt or covert age-related policies, then the numbers of the elderly receiving treatment would have slowly increased. Self-evidently none of this holds true. ARF disproportionately affects the old: biological and medical reasons for this can be proposed, but are difficult to conclusively prove. Even in those jurisdictions claiming universal health-care, intensive medical intervention is not infrequently withheld from the old (Hamel, Teno et al. 1999). This may result from decisions by doctors, carers or patients themselves. Age-determined restriction of access to advanced procedures and care became much less marked as time progressed, but remained an immeasurable factor tending to *reduce* the numbers of the very old in any collection of ARF cases. The conclusion must be that the concurrence of multiple disease and medical factors in the physiologically vulnerable has, in some indeterminate way, resulted in the modern expansion of the elderly within the ranks of those with ARF.

8.3b Location

Where does ARF occur? The patterns of causes of ARF arising in the community or in those already hospitalised differ in many respects. Community-acquired ARF includes trauma, abortion, many obstetric cases, infections, and accidental and self-administered poisonings. These were the predominant cases in Britain in the 1950s and 60s, and later in the developing world. In hospitalised patients, ARF follows medical or surgical treatment for pre-existing disorders or results from superimposed complications such as nosocomial infections. Hospital-acquired ARF increasingly dominated from the 1980s onwards and entirely accounts for the overall increase in numbers of patients, overshadowing the coincident decline in the frequency of community-acquired renal dysfunction. ARF arising outside the hospital tends to be preventable and have a potentially less severe course because the initiating catastrophe is more likely to be self-limiting. Conversely, hospitalised subjects inevitably carry a burden of co-morbidity, are less likely to be young, and the renal dysfunction is not infrequently the culmination of a series of adverse events.

In the 1950s and 1960s in the developed world the majority of cases of severe ARF developed from events occurring outside hospital (Derot and Legrain 1954; Bluemle, Webster et al. 1959; Alwall 1963; Balslov and Jorgensen 1963; Kennedy, Luke et al. 1963; Kirkland, Edwards et al. 1965; Kennedy, Burton et al. 1973; Turney, Marshall et al. 1990). Although slowly changing (Chugh, Sakhuja et al. 1989; Jha, Malhotra et al. 1992; Avasthi, Sandhu et al. 2003), ARF in third world countries continues to be

predominantly community-acquired (Adu, Anim-Addo et al. 1976; Rashid, Hossain et al. 1993; Cerda, Lameire et al. 2008). After a period of transition in which the proportion of hospital-acquired cases rose (Shusterman, Strom et al. 1987; Kleinknecht 1990; Turney, Marshall et al. 1990; Druml 1996) hospitals became the predominant site where ARF developed (Nolan and Anderson 1998; Lameire, van Biesen et al. 2005; Lameire, Van Biesen et al. 2006; Bagshaw, George et al. 2007) and, further, it is now within ICUs that the majority of patients are housed (Bellomo and Ronco 1996; Mehta, Pascual et al. 2004). The changing location of activity must be assumed to be a reflection of changing patterns of cause and perhaps more significantly an indication that the victims of ARF now have a greater pre-existing burden of disease.

This significant rise in severe disorders with poor outcomes cannot be simply explained on the grounds of demography alone. Although the number of older people has risen in all societies, the disorders in question have multiplied more rapidly and anyway it is usually contended that the elderly are generally healthier than previously. The causes of the documented increase in sepsis, ARF, and ventilatory failure appear to defy simple explanation. What should be of concern is that these potentially fatal complications arise for the most part in those already receiving technologically advanced treatment in hospital. They are clearly in some way interrelated and could, speculatively, be the consequence of some deep societal and medical changes. The pattern of disease and of intervention, must contribute in some as yet undefined way. ARF can again be taken as an indicator of a world in flux.

8.4 Epidemiology

It is usual for medical commentators to highlight the reduced frequency of 'simple' ARF as time has progressed, and this view has gained currency by repetition. The term 'simple ARF' has never been defined but has been assumed to include: a self-limiting or curable precipitating cause; the kidneys alone of all the organs have failed sufficiently to require mechanical support; the patient was previously fit and well without the burden of coexisting disease or advanced age. However, as repeatedly stated, ARF does not occur in isolation[227] and in all cases there is a precipitating event which itself requires treatment. Thus, while obstetric ARF is often retrospectively rather dismissively categorised as 'simple' because the patients were young and healthy, there can be no

[227] The exception to this is some types of primary glomerulonephritis in which the kidney alone is affected. However, many cases of ARF due to renal parenchymal disease occur in the context of a systemic disorder such as vasculitis or Goodpasture's syndrome.

doubt that gas gangrene of the post-abortal uterus infected with *Clostridium welchii* presented a total management challenge comparable to anything seen in the 21st century. Calling past cases of ARF 'simple' might be a convenient justification for the static, or worsening, mortality of the condition in the face of increasing medical endeavour, and might also be a facile phrasing obscuring the conflation of two separate conceptual problems. If the initiating event can be completely resolved and if the patient is not encumbered by other health problems, then the outcome will indeed be determined by the treatment of the renal failure. Conversely, dialysis can have only a limited impact in those situations where all manner of things are going wrong. One way of reviewing this is to determine whether 'simple' ARF has become replaced by more complex scenarios over time; that is, whether and why the epidemiology of ARF has changed.

ARF can potentially arise in almost any clinical situation. The triggering event is often catastrophic and life-threatening, but may be unexpectedly mild (for example, an allergic reaction to a common medication). Not infrequently, two or more factors coincide (Ali, Khan et al. 2007; Prescott, Metcalfe et al. 2007), each having an additive effect on the other to cause ARF: obvious examples would include postoperative sepsis or pneumonia treated with nephrotoxic antibiotics. Multiple causes, often leading to multiple organ dysfunction, appear to have become increasingly prevalent over time. This section seeks to explore whether, over the past 50 years, there has been a change in the causes of ARF, with an increase in the proportion of disastrous precipitants associated with or causing significant injury to other organ systems additional to the kidneys. Searching the evolving epidemiology of ARF may enlighten the question of the dissociation between increasing medical technological effort and proportionate measurable patient benefit. Additionally, it may inform the discussion of the trope that ARF represents the good, bad and indifferent of modern medicine.

A difficulty confronting analysis of the causes of ARF is presented by the tendency in the literature to lump multiple diagnostic categories within terms such as 'medical' or 'surgical'. As an example, the catch-all term 'medical' could include poisonings, cardiovascular events, non-surgical sepsis, primary renal disease, non-traumatic rhabdomyolysis, etc., etc. Surgery could include trauma, invasive intervention in any organ system, transplantation (although a few authors include this in 'medical' whilst others exclude it altogether), urological obstruction due to stones or prostatic hypertrophy, and malignancies of many sorts. To add to the confusion, patients requiring care in the ICU come from any and all specialities. Further, the criteria for admission to

ICU varied from time to time, place to place, country to country. This largely reflects availability of and investment in ICU facilities, thus about 3% of hospital costs in the UK but 30% in the USA are devoted to ICUs. Many, but not all, authors equate the use of mechanical ventilation with intensive care, but this is not necessarily the case in the USA where the proportion of ventilated patients may be less than 70%. The haziness of the definition is indicated by the often interchangeable adjectives of 'intensive' and 'critical' to describe the care of the sicker, more dependent patient. This is yet another variable confounding comparison of published series. These are more than a semantic issues as terminological inexactitude inhibits comparison between and understanding of published data. Despite these caveats, accumulated evidence shows that the prognosis of ARF is predictably determined by the number of other body organs that have also failed, however assessed (Cameron 1986; Liano, Junco et al. 1998; Angus, Linde-Zwirble et al. 2001).

	1950s	1960s	1970s	1980s
SURGERY	42.9	49.1	53.6	44.2
- General	88.5	68.2	77.8	34.05
- Cardiovascular	2.3	4.2	11.1	59.7
- Trauma	9.2	23	11.1	6.25
MEDICINE	31	34.7	40.5	55
- General	39.7	44	50	58.9
- Poison	11.1	24.5	17.6	18.7
- Renal Disease	49.2	31.5	32.4	22.4

Table 8.1. Percentage of subcategories within 'Surgery' and 'Medicine'.

8.4a Poisoning

The clearly identifiable categories of obstetrics and trauma are discussed in detail later because their changing significance enlightens the circumstances of the recent story of ARF. Other categories that can be dissected out of the general include poisonings and primary renal disease. At Leeds the number and proportion of poisonings (almost invariably self-administered) declined between the 1950s and the 1990s (Table 8.1), and the responsible agents changed markedly. In the early decades, aspirin and barbiturates

predominated; indeed, it was the success in removing toxic levels of these that helped to establish the utility of haemodialysis (Doolan, Walsh et al. 1951; Kyle, Jeghers et al. 1953; Danzig and Kringel 1955; Schreiner, Berman et al. 1955; Berman, Jeghers et al. 1956; Schreiner 1958; Honey and Jackson 1959; Schreiner 1990)Changing medical practice and protective legislation led to the disappearance of aspirin and barbiturates as suicidal agents and of carbon monoxide and carbon tetrachloride as deliberate or accidental intoxicants. In later years, paracetamol became the most prominent agent, causing ARF by direct nephrotoxicity or as a consequence of liver failure. In this case, the availability of antidotes, together with legislation affecting sales and packaging has also reduced the number of affected patients, in whom the clinical state was usually more complicated than that with some earlier poisons. Similarly, the increasing substitution of ethylene glycol in antifreeze has reduced the frequency of this most dramatic of poisonings (Peterson, Collins et al. 1981) in westernised countries. The same legislative protection rarely applies in developing countries where the use of cheaper but very toxic chemicals (for example, copper sulphate in India) remains widespread (Abuelo 1990). With some justification, poisoning is often dismissed as 'simple' ARF as the result of dialysis in many cases is dramatic. However, the deeply unconscious patient with drug-induced non-traumatic rhabdomyolysis or with ARF secondary to paracetamol-induced hepatic necrosis requires the full extent of ICU care, and faces the same poor outlook.

8.4b Primary Renal Disease

Many published series include primary renal disease (for example, rapidly-progressive glomerulonephritis) within the 'medical' category. Severe renal parenchymal disease may present as ARF, the patient prognosis of which is largely determined by the involvement of other organs (e.g. the lungs in Goodpasture's syndrome) and the complications of immunosuppressive therapy. The chance of renal recovery is determined by the extent of the damage caused by the primary disease and by the effectiveness of the therapy. Such patients constituted about 12% of the Leeds series, and involved all age groups with peaks in incidence in the young and the elderly. There has been debate about whether these aggressive immunological diseases have increased in incidence over time, perhaps peaking in the 1990s (Woodrow, Cook et al. 1990). What is not debatable is that comparing the 1950s and 1960s with the 1980s and later shows a remarkable improvement in prognosis (from c20% to >70% one-year survival). This has been due to prompt diagnosis by serology or biopsy, the availability of

aggressive immunosuppressive therapy to treat the primary disease and of long-term dialysis and transplantation for those with irrecoverable renal damage.

8.4c Iatrogenesis

It has been argued that the apparent rarity of ARF prior to World War II was because the very ill did not survive for long enough to develop ARF after their initial calamity. Changes in resuscitation, surgery, etc. allowed more to live to die later. While this is undoubtedly true, particularly in the context of successive major conflicts, there is also another feature of medical practice that resulted in increased frequency: iatrogenic ARF. Although later derided as useless, the regimen-based medical practice until the middle of the 20th century was at least relatively harmless. Arguably, the recent epidemic of ARF is mainly a consequence of medical intervention. Commencing with the sulphonamides in the 1930s, pharmaceutical developments produced an increasing number of drugs that whilst effective also effectively preyed upon the kidneys. That many of these drugs were specifically used for potentially serious conditions only enhanced their propensity to cause renal damage. The list of past and present drugs that have the potential to produce ARF is seemingly endless (Coggins and Fang 1988; Davidman, Olson et al. 1991) and notably includes medications in everyday use such as nonsteroidal anti-inflammatory drugs (Clive and Stoff 1984; Evans, McGregor et al. 1995). Drug-induced iatrogenic ARF can arise in a variety of ways:

- idiosyncratic allergic response (acute interstitial nephritis, most often with penicillins or diuretics);
- physico-chemical properties of the drug (crystalluria with sulphonamides or anti-virals);
- direct nephrotoxicity (aminoglycoside antibiotics, antifungals);
- mode of action of the drug affecting renal physiology (angiotensin converting enzyme inhibitors, cyclosporine, NSAIDs);
- secondary effects (tumour lysis syndrome in ill-prepared cancer patients receiving chemotherapy, diuretic-induced hypovolaemia).

The examples show that not only is there a large (and growing) list of potentially dangerous drugs but also that they are a relatively recent development: with the exception of the sulphonamides, none were developed before WW II and most are very much more recent, a feature of medicine after the mid-1970s. The inference is that pharmaceutical ARF is a relatively new, and expanding, phenomenon. The scope for iatrogenic renal disease is not limited to drugs. The use of radiocontrast agents in

diagnostic and interventional radiology mushroomed in the last quarter of the 20th century and these have considerable potential to distort renal function, especially in those made vulnerable by pre-existing diseases such as diabetes (Porter 1994).

Many iatrogenic cases result from inappropriate dosage of appropriate drugs, but this is by no means always the case and it is often difficult to apportion 'blame' in the cause of ARF. To take a hypothetical, but common, example: an elderly person, on long-term medication for heart disease, develops pneumonia and is treated with appropriate antibiotics, perhaps at a dose slightly too high for their age-related renal function. As their condition deteriorates, kidney function declines. What then 'caused' the renal dysfunction and which of the several factors (age, coexistent disease, sepsis, ARF) will determine the ultimate outcome?

Studies from the 1970s suggest that drugs could be implicated as the cause of about 10% ARF (Porter and Bennett 1980) and that antibiotics were the largest group involved. Figures for the 21st century are largely unchanged (MacEwen, Naik et al. 2011). However, in a major review Lameire (2006) estimated that drugs can be implicated as a contributory factor in 18–33% of hospital-acquired ARF. This accords with a population-based study which showed that 37.5% of cases were iatrogenic and/or preventable (Stevens, Tamimi et al. 2001). In specific groups such as haematological malignancies (Harris, Hattersley et al. 1991) and especially the elderly (Lameire, Matthys et al. 1987; Pascual, Liano et al. 1995; Kohli, Bhaskaran et al. 2000; Hsu, McCullough et al. 2007) the numbers of nephrotoxic ARF may be much higher. As well as the causative agents having changed with time, it would appear that the contribution of therapeutic agents to the genesis of ARF increased between the 1950s and 1970s, due to wider availability of potential nephrotoxins. From the 1970s onwards, the proportion of ARF cases to which drugs were at least partially contributory has remained constant (Elasy and Anderson 1996; Nolan and Anderson 1998). What this may say about the overall standard of medical practice can only be conjectured. One slight glimmer of hope is that drug-induced ARF is more likely to be of the form in which the urine volume is not greatly diminished (non-oliguric) and which tends to have a better prognosis, either because it is a 'milder' variety or because it creates fewer fluid balance problems and thus facilitates management (Anderson, Linas et al. 1977; Dixon and Anderson 1985). Iatrogenesis has caused increasing numbers of ARF over time and is an established if unwelcome feature of modern medicine, but has not necessarily contributed to the worsening outcome.

8.4d Surgery

The scope and complexity of surgical practice has changed radically since the 1950s. This changing activity continues and has been reflected in the narrow field of ARF. Overall, the proportion of surgical cases remained stable from the 1950s to the turn of the century, but this generalisation obscures the increasing number of cardiovascular cases which replaced the earlier general surgical problems.

Cardiac surgery using prototype bypass machines was a rare event until the late 1960s or 70s, and was limited to congenital heart problems or advanced rheumatic valvular disease. Severe ARF developed in about 5% of the operated patients, and carried a mortality of 80-100% (Cameron and Trounce 1964). The widening application of surgery to include the much more numerous cases of coronary artery disease, together with sophisticated and much safer (because of pulsatile perfusion) commercial bypass technology meant that cardiac surgery became a frequent routine in a broader group of patients. Advances in both technology and technique allowed more complicated surgery, and hence prolonged duration of circulatory assist, in more vulnerable patients. Later studies included thousands, not tens, of patients (Rosner and Okusa 2006). In the 1990s the incidence of severe ARF following cardiac surgery was about 1% with a mortality of up to 70%. Despite the reduced risk of developing postoperative renal dysfunction, the large numbers operated on meant that cardiac surgery became a significant cause of ARF, as shown in the Leeds series.

This epidemiological data obscures several facets of renal dysfunction following cardiac operations, mainly relating to the changing demography and type of surgery. A comparison within a single unit (Ostermann, Taube et al. 2000) between the late 1980s and the late 1990s showed that the frequency of severe ARF declined and mortality significantly improved despite the fact that the patients were older and underwent more complex surgery (and hence spent longer on bypass, a known risk factor for the development of ARF). By the late 1990s, surgery was confined to more complex coronary lesions, those requiring repeat or emergency intervention or combined valvular surgery. The majority of more straightforward cases had come to be treated by off-pump surgery or percutaneous angioplasty, a less invasive procedure made possible by commercial technical developments. Surgery was performed less often but in increasingly at-risk patients. Nevertheless, results appear to have improved.

The large numbers of patients within a definable category has allowed extensive statistical analysis of the inter-relationships of postoperative renal dysfunction. The

development of dialysis-dependent ARF is associated with at least a 10-fold increased risk of death (very much higher in some studies). However, even minor perturbations of renal function, insufficient to warrant intervention, are associated with an increased mortality (Lassnigg, Schmidlin et al. 2004). The excess deaths appear due to a greatly increased susceptibility to acquired infection (Thakar, Liangos et al. 2003; Thakar, Yared et al. 2003; Thakar, Worley et al. 2005). Patients who develop postoperative renal dysfunction also experience increased mortality following eventual hospital discharge (Lok, Austin et al. 2004; Loef, Epema et al. 2005). One could interpret these observations as indicating that ARF is a measure of the comorbidity of the patients, who are older and self-evidently have generalised cardiovascular disease. It could be said that acute renal dysfunction is the identifiable tip of the iceberg of chronic ill-health, the ARF acting as a warning signal when the system is stressed by, for example, surgery.

A significant minority of survivors post-cardiac surgery never regain independent renal function, and their subsequent prognosis is extremely poor (Leacche, Rawn et al. 2004). This pattern is repeated in survivors of aortic surgery (Bhandari and Turney 1996; Barratt, Parajasingham et al. 2000). The mortality of ARF following vascular surgery is variously reported to be between 10% and 75%, the risk being highest following emergency surgery (Berisa, Beaman et al. 1990). Disease of the thoracic or abdominal aorta of such severity as to warrant surgery is inevitably associated with systemic vascular disease, including of the renal arteries. Again, ARF may be thought of as a consequence of technically heroic surgery in vulnerable elderly people.

Whereas it is possible to map changing patterns in some sub-categories of ARF, the catch-all divisions of ‘medical’ and ‘surgical’ rather defy analysis because of lack of detail or of chronology in most publications. These portmanteau terms include such a medley of disparate patients and conditions as to defy detailed analysis of the shifting patterns of causation. Identifiable sub-groups within each category reveal anomalous results: despite increasing surgical activity the number of cases of ARF has declined over the years and outcomes have improved. Following the fortunes of ARF caused by such as obstetrics, trauma, cardiac surgery or renal parenchymal disease does not provide an obvious answer to the perennial question of why the mortality of ARF has worsened. The excess mortality in later years appears to be borne by an expanding uncharacterised group, a hotchpotch of broadly medical or surgical patients. Complexity is exacerbated by ‘sepsis’ and ‘ventilation’, categories which cut across the classification by cause system and which are the greatest difference in the pattern of ARF then and now. It may

well be concluded that from, say, 1990 there existed two distinct patterns of ARF: a growing number of patients with multiple organ failures in the ICU, and another group with almost exclusively one-organ failure, whose pattern does not differ greatly from that 50 years ago.

8.5 Socio-economic factors

The suggestion that both the incidence and the causes of ARF are influenced by lower socio-economic status (Chugh and Singhal 1982) is supported by the relatively high incidence in rural populations in developing countries (Jha, Malhotra et al. 1992) who not only develop ARF from causes peculiar to them (snakes, agricultural chemicals, traditional remedies and, especially, malaria) and their society (septic abortion, the rate of which appears to be worsening), but also lack good medical facilities, to which access may be restricted on grounds of cost, distance or even culture (Cerda, Lameire et al. 2008). Some support for this view is provided by the higher incidence (and poorer outcomes) in Black Americans (Obialo, Okonofua et al. 2000) and South Africans (Seedat 1982; Seedat and Nathoo 1993). The epidemiology and demography of ARF in the third world have changed over time, but at a slower rate than in developed countries (Chugh, Sakhuja et al. 1989). Factors influencing this may include increasing urbanisation and economic improvement, legal medicalization of abortion, reduced preventable problems such as diarrhoeal diseases. The young patient with single-organ kidney failure has been replaced by the older patient with multiple complex problems, just as in the West. The argument that economic development is the root cause of the changes in ARF in all countries has been imaginatively developed (Liano and Pascual 1998) and is represented in Figure 8.4. Whilst this deterministic scenario is not unreasonable, it does not address some key issues: exactly why are there more patients who are sicker, particularly with sepsis?

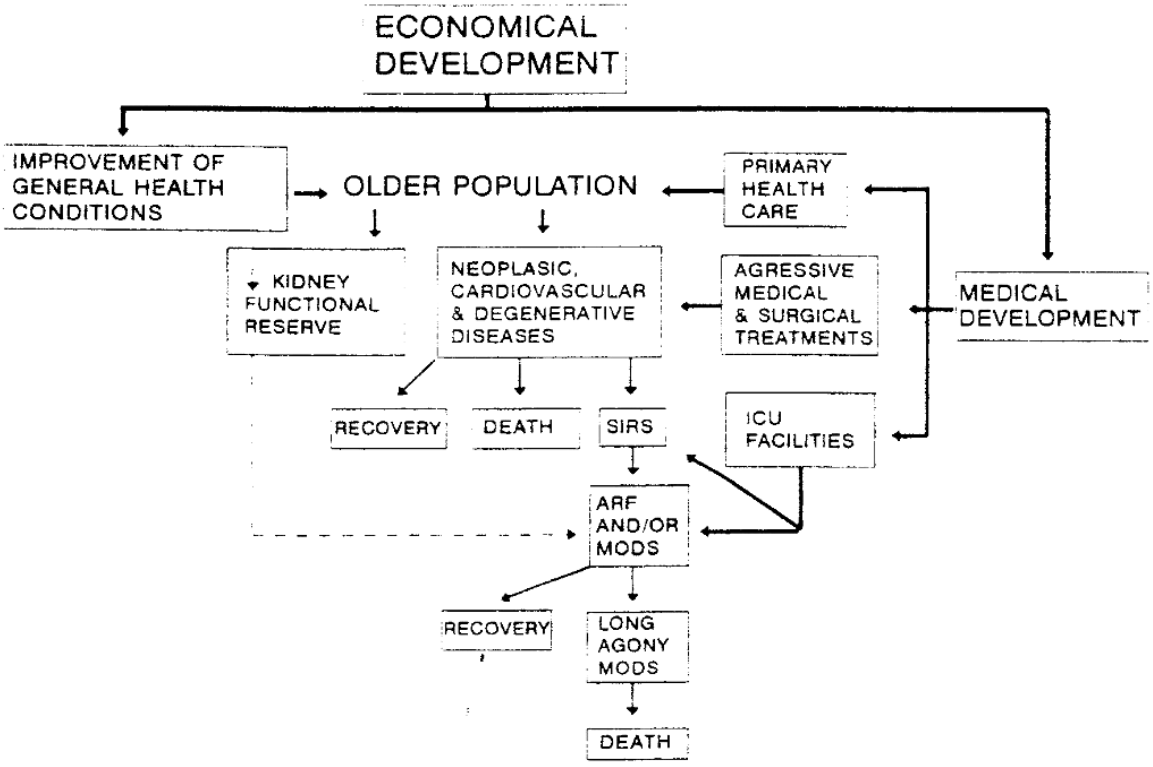

Figure 8.4. Postulated Interaction of Socio-economic Factors in Critical Illness

(SIRS: Systemic inflammatory response syndrome
MODS: Multiple organ dysfunction syndrome)

8.6 Changing outcomes

I have suggested that nephrological introspection was triggered by the suggestion that their activities had resulted not in improved patient outcomes but rather that the picture had deteriorated. The answer then was believed to be that patients were becoming older, that their general medical condition was deteriorating and that the precipitating causes were becoming more serious. This composite explanation held credence thereafter, and most of the published evidence was directed to confirming this assumption.

From the earliest days of treatment for ARF, mortality has been taken as the endpoint for assessing therapeutic efficacy. Death has some advantages as a statistic: it is unequivocal and of obvious paramount interest to the patient. The use of this as a measure does, however, beg the question of what is the proximate cause of death in any individual (Woodrow and Turney 1992). This has relevance because the death may be due to the acute disease itself, shortcomings in therapy, superadded complications, co-morbidity or indeed any or all of the above. Nephrologists liked to say that patients no longer died **from** ARF but rather died **with** ARF. This claim was based on the obvious

fact that patients may die despite blood biochemistry having been improved or even normalised by dialysis. What it really shows is a naively restricted understanding of the complexity of the ARF syndrome. Statistically (and from the patient's viewpoint) the result was the same, but the specialist could shift the responsibility elsewhere. From perhaps the 1990s it was increasingly accepted that simply surviving was not necessarily the only desirable outcome of intensive care, but that rehabilitation, future life expectancy, and long-term disability were of great importance to survivors and should be measured as part of outcome assessment. The view that quality as well as quantity of life was important was brought into sharp focus when the ethics of aggressive medical intervention were questioned. In the context of ARF, permanent recovery of independent renal function was of particular importance. In a world of diminishing resources and increasing demand, it is not unreasonable to consider the costs of both successful and unsuccessful interventions.

Overall mortality in ARF has increased with time. Ympa and colleagues sought to minimise the confounding variables of management and case-mix by combining all published series to analyse 16,000 ARF patients reported between 1956 and 2003 (Ympa, Sakr et al. 2005) and showed that mortality rose throughout this time (Table 8.2). This general picture contrasts somewhat with the experience at some centres. For example at Leeds (Turney 1994) and elsewhere (Biesenbach, Zazgornik et al. 1992; McCarthy 1996) mortality fell, at least until the 1990s, but may have later increased because of the expanding numbers of critically ill ICU patients.

An apparent anomaly in both individual and and compound series is that mortality during the 1970s was higher than in the preceding or succeeding decades. It cannot be coincidental that this was the time in which nephrologists started soul-searching over their results. But what made the 1970s different and how might this inform later events? Although it had been possible to maintain patients indefinitely on dialysis from the early 1960s, in reality the numbers of treated ESRD patients then were small and it took time for the investment in people and facilities to gather momentum and for the hidden demand for chronic dialysis to become manifest. In the UK and the USA, expansion of the number and size of units did not take place until the 1970s, and at least in the UK did not keep pace with demand. Consequently, existing facilities rapidly became overstretched and perforce concentrated their energy, attention and resources on the chronic patients at the expense of the acutes (Cameron 2002). As has been discussed previously, a consequence was resurgence in the use of peritoneal dialysis, which proved

less than efficacious for the newly-presenting catabolic critically ill patients. Changes were also occurring outside nephrology, the most relevant being the expansion of ICUs in which congregated the most vulnerable patients, often the recipients of increasingly adventurous surgery. The 1970s was a pivotal decade in which older and sicker patients met overtaxed facilities, with disastrous results. However, recognition of an unacceptable state of affairs did refocus attention and probably resulted in subtle and additive changes in both intensive care and renal support, the sum of which was an improvement in outcomes which appeared to at least keep pace with the deteriorating medical status of these patients.

YEARS	% MORTALITY
1956-60	42
1961-65	47
1966-70	49
1971-75	63
1976-80	61
1981-85	51
1986-90	52
1991-95	55
1996-2003	57

Table 8.2 Mortality of ARF from Published Reports

(Ympa, Sakr et al. 2005)

		ARF	ARF + DIALYSIS
Incidence	1988	61	4
/100,000 population	2002	288	27
Mortality	1988	40.4	41.3
(%)	2002	20.3	28.1
Comorbidity Index	1988	16.4	
	2002	26.6	

Table 8.3 ARF in the USA

(Waikar, Liu et al. 2008)

A study (Waikar, Liu et al. 2008) of US discharge data identified 5.5 million discharges coded for ARF between 1988 and 2002, of which nearly 600,000 received dialysis. Not only had ARF greatly increased in incidence but also mortality had decreased, despite an increase in the calculated co-morbidity index:The inference from this study is that ARF patients have truly increased in both number and severity of illness, but that this has not necessarily resulted in a worsening of outcome. A measured and acceptable explanation for this apparent conundrum is not readily forthcoming.

Beyond merely considering the death rate associated with acute renal dysfunction, patient outcomes can be looked at from two rather different angles to attempt to assess the impact of ARF then and now: to what extent does the development of ARF affect the outcome of the underlying problem and does the timing of the onset of ARF tell us something different? The answer to the first has always been unequivocal: the development of even minor degrees of kidney injury greatly increases the mortality and costs of the primary disease or procedure (Levy, Viscoli et al. 1996; Turney 1996; Chertow, Burdick et al. 2005). Relevant information was thin until the widespread use of computing to gather and analyse data and to measure effects and risks. The development of ARF increases the risk of dying 3–10-fold in any group of patients (Yegenaga, Hoste et al. 2004; Chertow, Burdick et al. 2005; Uchino, Bellomo et al. 2005) and by even more in some, such as following cardiac surgery (Liano and Pascual 1998). It is not clear why there should be an excess mortality associated with renal dysfunction insufficient to require dialysis. Acute deterioration in kidney function associated with radiocontrast use is followed by (but does not cause) excess long-term mortality (Goldenberg, Chonchol et al. 2009). The inference is that the development of ARF is a measurable indicator of an individual's precarious medical state, whether due to advanced age or sub-clinical organ dysfunction.

Further evidence that ARF should now be regarded as an emblem of severity of illness and not necessarily a discrete entity in modern multiply beset patients is provided by the timing of the onset of the episode of ARF. From about the 1980s, hospital-acquired ARF increasingly dominated that developing in the community (Nolan and Anderson 1998). For patients requiring care in the ICU, the prognosis of ARF already present at admission is significantly better than if it develops later in the course of their multisystem illness (Lameire, van Biesen et al. 1999; Guerin, Girard et al. 2000; Lameire, Van Biesen et al. 2006; Lameire, Van Biesen et al. 2006). It has also been noted that should ESRD dialysis patients be admitted to ICU for an intercurrent problem,

their outcome is not noticeably different from that of age- and severity-matched patients with normal renal function. This suggests that kidney function *per se* and the need for dialysis do not necessarily determine outcome, but rather that the acute episode is part of a wider picture which may be called "the slippery slope of critical care" (Breen and Bihari 1998).

Thus far, mortality has been considered only in the short-term, essentially death during the hospital admission in which the acute episode occurred. The continuous series, from 1956, of patients treated at Leeds allowed prolonged follow-up (Turney 1990; Turney 1992). This showed that, following the initial in-hospital mortality, there were further excess deaths over the next year or so from associated conditions such as malignancy. Thereafter the life expectancy of the survivors did not differ from that of the general population. There was, of course, a bias in the Leeds data which tended to make this good prognosis a historic rather than a contemporary result: there was a preponderance of young people with single-organ renal failure and limited co-morbidity during the 1950s and 1960s and this would undoubtedly have favourably skewed the 30-year follow-up. Thus it was shown, for example, that the survivors of obstetric ARF went on to lead lives normal in every respect.

Although there are no studies that are comparable in size and duration, there are a few that suggest that the medium-term (1-5 years) outlook is now not as good, due mainly to greater age at the time of the (more severe) critical illness. For example, ICU patients with ARF have only a 20% 5-year survival (Morgera, Kraft et al. 2002; Morgera, Schneider et al. 2008). But, to put it another way, about 50% of those who survive the initial insult are alive at 5 years. This compares with the results of other studies of ARF (Ahlstrom, Tallgren et al. 2005) but extended survival is less good than for pneumonia treated in the ICU (Ranes, Gordon et al. 2006). It would appear, therefore, that the long-term prognosis has also changed over the years and has become more guarded than before, perhaps worsened by the increasing frequency of failure of recovery of renal function in survivors (see below). It may be assumed that this restricted longer-term survival is dictated not by the episode of acute kidney dysfunction but primarily by coexistent chronic health problems. There are, however, no data on the causes of the later death, so any conclusions can be only speculative.

What have patients with ARF died from over the years? A review of 636 deaths at Leeds up to 1990 (Woodrow and Turney 1992) showed that death was increasingly ascribed to cardiovascular events, reflecting increases in both the age of the patients and

the numbers undergoing cardiac surgery. Preventable causes, such as gastrointestinal haemorrhage and withdrawal of dialysis disappeared. About 40-50% of deaths were due to infection, in 70% of which the sepsis was present at the onset of the ARF. That pre-existing or acquired sepsis is the single largest cause of death has been repeatedly confirmed (Beaman, Turney et al. 1987; Liano and Pascual 1998; Akposso, Hertig et al. 2000). Overall, by the end of the period the majority of deaths could be attributed to the underlying or associated disorders. The remainder had acquired fatal complications, predominantly sepsis, during the course of the episode of ARF. This pattern of co-morbidity as the proximate cause of death has persisted (Liano and Pascual 1998) and is the reason that nephrologists continue to claim that nobody dies of ARF and its direct complications, but rather from other problems. More seriously, if the cause of the high mortality is largely due to the underlying diseases, of which ARF is but a complication, then a brighter outcome can be achieved only by attention to these disorders and not by further refinement or increased application of the renal technology.

8.7 Recovery and rehabilitation

A crucial part of the original definition of ARF was the capacity of the kidneys to fully recover function after the acute episode. Indeed, this was so critical to the early adoption of dialysis that it became a central tenet of both theory and practice. Apart from the occasional case of acute cortical necrosis, almost invariably associated with obstetric disasters, this proved true until the late 1980s when there was a hint that a small number of survivors never regained freedom from long-term dialysis (Corwin and Bonventre 1989). The Leeds experience provided an analysis of the 651 survivors (59.5% survival) of the latest 1095 patients dialysed for ARF in the absence of pre-existing renal disease (Bhandari and Turney 1996). Of these survivors, 16.2% remained dialysis-dependent. That is to say, the degree of renal damage had been so great as to preclude meaningful restoration of function sufficient to allow an independent existence. Furthermore, the frequency of non-recoverable renal injury had doubled from 10.2% in the 1980s to 20.4% in the 1990s. The prospects for these now ESRD patients was poor: their survival on long-term dialysis was significantly worse than for the general ESRD population, largely due to excess cardiovascular mortality (in fact, the survival of these patients was worse than that usually quoted for most malignancies). This large and increasing number of permanently dialysis-dependent patients has been confirmed by later studies (McCarthy 1996; Noble, MacKirdy et al. 2001; Metcalfe, Simpson et al. 2002; Morgera, Schneider et al. 2008; MacEwen, Naik et al. 2011) and some of these report an even

higher percentage among survivors of ICU (Liano and Pascual 1998) or vascular surgery (Barratt, Parajasingham et al. 2000). Those who do not recover independent renal function spend about twice as long in hospital as do those with only temporary renal failure. Additionally, they incur much greater post-discharge health care costs, not least because of continuing dialysis-dependence (Manns, Doig et al. 2003).

If an individual contrives to survive ARF and avoid permanent dialysis, what chance is there of full rehabilitation? Whereas the earlier impression was of full, or nearly full, rehabilitation (Turney 1992), the later literature unequivocally suggests that quality of life is determined by both age and the severity of the precipitating illness, both of which have altered over time. Thus, unlike in the 1950s or 1960s, the majority of survivors of ARF in the ICU are significantly impaired, leading to an estimate of 15 QALYs gained per 100 patients treated (Ahlstrom, Tallgren et al. 2005). The cost of each QALY gained was calculated to be $128,000 (range $61,900 for the best prognosis patients to $274,100 for the worst prognosis group) in 1997 (Hamel, Phillips et al. 1997).

Costs can be calculated in different ways, and the results are often eye-watering. For severe sepsis (Angus, Linde-Zwirble et al. 2001) the cost per case was $22,100 at 1995 prices, compounding to $1.6 billion annually for the whole of the USA. For these and for ARF, the extreme costs are generated within the ICU, and the length of stay within ICU for both survivors and non-survivors appears to have progressively increased from about 10 days in the 1980s to 20+ days after 2000 (rather less in British ICUs). The greatest costs are expended on a minority of patients, those who are most severely ill but who have not died. The cost per survivor of ICU was estimated at ~$100,000 in 1990 (Daly and Bihari 1998). Inflation in health care systems is often said to exceed 10% per annum, but evidence shows that in ICUs the annual increment is at least double this. A major factor leading to additional ICU stay is the increased numbers of the elderly, who take longer to be weaned from ventilation and to be discharged, whether or not ARF has occurred (Ely, Wheeler et al. 2002). If only a minority live to hospital discharge, the cost per survivor is potentially astronomic.

8.8 Obstetrics: A summary example of the history of ARF.

The history of ARF associated with pregnancy-related mishaps may be considered to reflect the history of ARF in microcosm. It illustrates the interaction of medical and social factors in defining the disease entity, the interrelationship of ARF and its technology, and the external influences that changed the epidemiology of ARF.

The potential adversities facing the pregnant woman may be both special and general – the circulatory changes and the partial immunological tolerance are specific to pregnancy, but haemorrhage and sepsis are not necessarily so. Thus the many faceted eclampsia syndrome (Grossman, Hamilton et al. 1974; Koffler, Friedler et al. 1976; Gabow, Kaehny et al. 1982; Honda and Kurokawa 1983; Dubrow and Flamenbaum 1988; Veenstra, Smit et al. 1991; Zager 1996; Holt and Moore 2001) is unique to pregnancy and displays many of the features of the classic immunological experiment known as the Schwartzman reaction. Haemorrhage, before or after delivery, may be catastrophic and cause shock, but uniquely may also be 'concealed' causing placental separation with fetal death and breakdown of the placental barrier triggering a cascade of reactions to which the kidneys are particularly sensitive. The particular physiological and immunological milieu of pregnancy probably explains the more frequent occurrence of the most extreme form of ARF, bilateral cortical necrosis, although this is by no means gestation-specific.

Obstetric ARF was the first form of the condition to be described in the medical literature from about the turn of the 20th century (Bradford and Lawrence 1898; Lloyd 1906; Klotz 1908; Torrens 1911; Jardine and Kennedy 1913; Rolleston 1913). The description was essentially of scattered case reports of catastrophes followed by fatal kidney failure, the histology of which was predominantly cortical necrosis. It was seen as a rare but dire complication of obstetric disasters, despite its description in association with other events such as severe sepsis. This apparently clear sequence was gradually questioned because of two observations. Firstly, there were clinically identical cases that dramatically did not die because their kidneys spontaneously more or less recovered, a result incompatible with the accepted knowledge of cortical necrosis (Madding, Binger et al. 1940; Young and McMichael 1941; Young 1942). Secondly, sometimes the renal histology (obtained at post mortem or from surgical intervention such as capsulectomy (Roberts and Barker 1892; Parkes Weber 1909; White 1918; White 1918-9)) showed intact cortices and a strange appearance of tubular destruction. This was not immediately compatible with the then current thinking on renal histology, based as it was on terminal, usually chronic, disease. These two pieces of information were not intellectually connected and certainly did not impinge on the wider medical community, for whom what became known as ARF then appeared to be a vanishingly rare event. There had, however, been recognition of potentially recoverable renal failure with similar anatomical appearances following poisoning (Outerbridge 1923). In particular, mercuric

chloride was increasingly used as an abortifacient, again suggesting that this was a specific event largely confined to obstetrics and thus a ‘special’ case without wider implications

The potential for acute kidney injury from a critical event was brought into sharp focus by the description by Bywaters and Beale in 1940 of what they initially thought was a new clinical entity: the ‘crush syndrome’. Almost instantaneously it was suggested that an identical condition had long been known in obstetrics and that whatever the precipitating event the final common pathway was necrosis of the renal tubules. Despite some disagreement over nomenclature, the accepted picture of ARF was constructed, largely by morbid anatomists who synthesised clinical features and pathological appearances into a coherent discrete clinical entity. With the cessation of hostilities, ARF lost its immediacy because of its relative infrequency in most branches of medicine apart from obstetrics.

It is not possible to determine whether there was a real increase in the frequency of obstetric ARF from the mid-1940s, or whether the establishment of centres with an interest and expertise in renal failure attracted the referral of cases that would otherwise have expired in anonymity in peripheral hospitals. Certainly referral hospitals in New York and Boston (Swann and Merrill 1953), Paris (Derot and Legrain 1954; Grunfeld, Ganeval et al. 1980), the Hammersmith (Bull, Joekes et al. 1955; Bull, Joekes et al. 1956) and Leeds (Parsons 1962; Parsons 1963) all found that a significant proportion (perhaps a third or more) of their patients had ARF precipitated by obstetric accidents or complicated induced abortions. The disproportionate representation might well have arisen from positive and negative, as well as medical and social, selection.

Negative selection arose in two ways: older patients were not usually considered for active intervention, which tended to be restricted to those below the State retirement age until about 1980. This appears not to have been a defined policy, merely an untested assumption that the elderly would not ‘benefit’ from major surgery or dramatic medical treatment. Medical practice changed over time, the patriarchal ageist withholding of treatment becoming unacceptable, largely as a result of societal pressure. This partly contributed to the rising age of ARF patients, for example at Leeds the median age increased from about 40 years in the 1960s to 65 in the 1980s. If an age-related selection policy was imposed, and there is no means of knowing which and how many referrals were refused, there would be disproportionate selection of the young women with obstetric ARF. Positive selection of young obstetric patients could have been driven by

the emotional impact of a critically ill mother who would have invariably have lost her baby. The momentum to do everything possible was further stimulated by the increasing, and increasingly formalised, surveillance of obstetric services in which, at least in the British NHS, the responsible clinician was obliged to report in detail on, and be independently investigated for, every maternal death.

The frequency of ARF following abortion is even less clear. Its illegality inevitably means that good data are lacking, but procured terminations were by no means uncommon (James 1971; Goodhart 1973; Lane 1974; Brookes 1988). Perhaps half the pregnancy-related cases in Leeds, Boston and Paris followed septic instrumental abortion, which had become more openly acknowledged by the medical profession rather than disguised in hospital statistics as 'spontaneous' abortion or miscarriage, or some sort of abdominal sepsis (Loudon 1992; Loudon 1993). Correspondence over many years in the journals and the lack of medical resistance to the principle of the 1967 Abortion Act suggests that the profession was increasingly accepting of the reality of the situation and so less likely to restrict treatment. Nevertheless, there was obvious sensitivity on this subject: for several years the Mount Sinai Hospital, New York disguised the fact that their first dialysis survivor had been a septic abortion.

It might be argued that the preponderance of pregnancy cases between, say, 1945 and 1970 in the UK reflected obstetric practice then obtaining as well as a paucity of victims of later more invasive medical procedures. Whatever the convergence of reasons, the high proportion of ARF cases from obstetric causes had a significant, if not critical, influence on ARF and its therapy. These were previously healthy young women and, in many cases, the cause of the ARF had been resolved by delivery of the products of gestation. Later commentators were to categorise such cases as 'simple' ARF, which is simply recoverable renal impairment unencumbered by comorbidity, advanced age or on-going primary disease. In retrospect, they were expected to have a good prognosis although this was, of course, unknown at the time. Those who later criticised the 'conservative' approach to management contended that by selecting such favourable cases, the dietary regimen was made to look more effective than it might have been in more complicated cases. However, I have earlier suggested that any selection of cases could well have been only partial and that the epidemiology of the time favoured more straightforward situations which did indeed enhance the results not only of conservative treatment but also, later, of dialysis.

Thus in the Hammersmith obstetric series (Bull, Joekes et al. 1955; Bull, Joekes et al. 1956) of 33 reported patients, average age 30 years and managed by diet, there were 8 (24.4%) deaths. However, about one third of the patients were never oliguric. Of Parsons' first 100 dialysed patients, 25 were obstetric and he reported a single death (4%) (Parsons and McCracken 1959; Parsons 1962; Parsons 1963). Between 1956 and 1969, Parsons dialysed 131 obstetric cases (of a total of 794) with a survival of >80%, compared with 49% in all his ARF patients (Turney, Ellis et al. 1989). Both centres cited the obstetric results as vindication of their treatments, but the impact of Parsons' data was immeasurably greater. It is hard to overstate the effect of the reported results on the general attitude towards and acceptance of dialysis. The use of dialysis during the Korean War is usually thought to be the point at which the machine proved its worth by halving the otherwise inevitable mortality of post-traumatic oliguria. That event also had dramatic and patriotic undertones. However, the even more impressive results obtained in obstetric cases had a greater impact on medical attitudes. This was most apparent in Britain, where Parsons' successes effectively converted a previously sceptical audience. The influence of the eye-catching survival figures (Jackson 1963) was reinforced by the accumulating evidence that the survivors subsequently lived entirely normal lives, with complete restoration of kidney function (Elliott, Ashcroft et al. 1964; Turney 1990; Turney 1992). Based solely on the obstetric results, dialysis could be promoted by its enthusiasts as the panchreston of the failed kidney. The counterfactual question of when or whether dialysis would have been accepted without the encouraging results in obstetrics remains open.

Pregnancy-related ARF became rare in the Western world from c1970 (Stratta, Besso et al. 1996). It remains a significant cause of maternal death in undeveloped countries and in those without legalised medical abortion (Silke, Carmody et al. 1980; Date, Raghavan et al. 1987; Pertuiset and Grunfeld 1994; Stubblefield and Grimes 1994; Randeree, Czarnocki et al. 1995; Vladutiu, Spanu et al. 1995; Naqvi, Akhtar et al. 1996; Ventura, Villa et al. 1997; Nzerue, Hewan-Lowe et al. 1998; Selcuk, Tonbul et al. 1998; Brown 2007): for example causing about 25% of ARF cases in Nigeria (Bamgboye, Mabayoje et al. 1993) and Argentina (Firmat, Zucchini et al. 1994) and more than 50% cases in Ethiopia result from septic abortions (Zewdu 1994). In all these countries, the mortality of obstetric ARF remains at about 35-50%, partly because of late referral of abortion cases and partly because the women are reluctant to give a full history, thereby delaying diagnosis and proper treatment. The implementation of a Medical Termination

of Pregnancy Act in India reduced the incidence of abortion-related ARF from 22% in the 1960s to 8% in the 1990s. That there are still cases in India reflects cultural and economic pressures on women. These same factors might also explain the persistently high incidence of abortion- and obstetric-related ARF, with poor survival, amongst Blacks in South Africa (Seedat 1978).

In Britain, septic illegal abortion suddenly and completely disappeared after the implementation of the Abortion Act in 1968. The application of asepsis and the avoidance of douches, inappropriate instrumentation, and toxic abortifacients completely removed a significant public health issue. In this respect, ARF can be considered a marker of social change. The data however indicate that obstetric ARF was declining in absolute and relative frequency before the legalisation of abortion. The incomparable Leeds series shows that, despite an increasing overall workload, obstetric cases more than halved in absolute numbers and in proportion before the Abortion Act. This partially explains the previously mentioned increase in age and, presumably, the progressively declining survival. The increasing rarity of obstetric cases must be regarded as true and not an artefact of the increasing representation of older patients with complex medical and surgical conditions. The epidemiological changes reflect changes in medical practice, most particularly in relation to effective resuscitation achieving rapid restoration of circulation and, in obstetrics, early and aggressive intervention in eclampsia. Changes in neonatal practice allowed the delivery of premature infants, with a reasonable prospect of survival, as soon as maternal complications became apparent; these potential complications being detected earlier because of improved monitoring and screening of pregnancy.

From the 1970s less than 1% of severe ARF in developed countries has been pregnancy-related, but the survival of these rare cases is significantly worse. Medical and social changes had prevented the uncomplicated good-prognosis cases, leaving a rump of severely ill patients with complex underlying disorders, for example autoimmune diseases such as systemic lupus erythematosus or the anti-cardiolipin syndrome. The prognosis therefore came to be determined not by the acute renal dysfunction *per se* but by the comorbidity. Again, obstetric ARF reflected the trend in ARF as a whole of increasingly complicated cases in whom, despite unprecedented commitment of medical resources, survival appears worse than 50 years previously. A further change, in both obstetric and general ARF, is that it is no longer a given that survivors will regain normal kidney function, a substantial number remaining

indefinitely dialysis dependent (Bhandari and Turney 1996). Outcome is no longer determined by the management of the kidney failure because ARF became just a facet of multiply deranged physiology, a marker of whole body dysfunction.

Obstetric-related ARF is a largely forgotten condition in the developed world but remains an ever-present threat to maternal health in non-westernised countries (Ronsman and Graham 2006). It is preventable, but prevention requires profound cultural and societal changes and also accessible advanced medical facilities. Its historical significance lies in the good results reported for dialysis which justified the continuing use of the technology. I have offered obstetric ARF as a circumscribed example of the history of ARF, its effects on technology and practice, and to indicate that this history reflects medical and social changes.

8.9 Traumatic ARF: Changes with time and geography

Whether or not an individual develops ARF following trauma depends on the extent of blood loss and tissue damage, the speed and completeness of resuscitation, the development of complications such as sepsis, and the age and constitution of the victim. Thus, ARF is a measure of both injury severity and the effectiveness of medical intervention. The latter in turn depends on accumulated understanding of the physiology of shock, the availability of suitable intravenous fluids and trained medical personnel, and the technical development of monitoring and delivery equipment. But the risk of actually suffering trauma is socially determined: warfare, criminal violence, risk-reduction measures in industry or on the roads, preparedness for natural disasters such as earthquakes. It follows that post-traumatic ARF also provides an illustration of ARF as a marker of social and medical events and behaviours.

The Leeds series (Guly and Turney 1990) provides an indicator of the social environment: it is a civilian practice in Britain, which has (despite the efforts of the popular press to suggest otherwise) a very low frequency of gun and knife crime; the series is long enough not only to cover the period of the decline and disappearance of heavy industry and coalmining[228] in northern England, but also the implementation of improvements in the safety of motor vehicles and, significantly, the organisation and practice of the emergency management of victims of multiple trauma.

[228] Crush injury from mining accidents was recognised soon after Bywaters' publication (Caplan, A. and G. E. Dunkerley (1945). "Traumatic anuria in a miner." Lancet **1**: 147-148.) and indicated the applicability of ARF to civilian practice. In fact for the period between the end of the London Blitz and the start of the flying bombs, Bywaters' MRC unit on crush was transferred to Newcastle to investigated injuries in mining and heavy industry. It is believed that they encountered little clinical material.

As with obstetric cases, the total number and proportion of trauma patients declined over the period of activity of the LGI renal unit, from about 10% of the total patients in the 1960s becoming rare (<1%) from the 1980s onwards. Mortality altered little over the period, being around 45% in all decades, but the Injury Severity Score and the age of the patients both markedly increased with time. That is to say, the less severely injured (and hence the most likely to survive) patients had been selected out by preventative emergency treatment, leaving the less frequent but iller ones to skew the outcome. If, under these circumstances, the mortality remained more or less static, the inference could be that the total management of ARF was improving. The British experience, however, does not completely reflect that obtaining elsewhere. Globally, trauma remains a major cause of ARF, relating to the higher incidence of violence (for example, perhaps 20% of trauma victims in the USA have gun-shot wounds, whereas in Leeds over 50 years there was but a single case, and that due to a misdirected suicide attempt) and the carnage on the world's roads, particularly in developing countries (Ameratunga, Hijar et al. 2006).

The history of ARF is inextricably entwined with that of 20th century conflict. From its original description in World War I to its re-discovery by Bywaters and Beal during the London Blitz, crush injury has had a centrality in the thinking about ARF, its pathology (Husfeldt and Bjering 1937; Dunn, Gillespie et al. 1941; Oliver, MacDowell et al. 1951), treatment (Bywaters and Joekes 1948) and its potential for recovery (Anon 1941; Blackburn and Kay 1941; Henderson 1941; Longland and Murray 1941; Maitland 1941; Bradley 1942; Scott and Rob 1947). One of, if not the, medical "benefit" of warfare is the opportunity to study and treat large numbers of relatively uniform cases. Arguably, this has proved true in no context more than ARF (Butkus 1984), highlighted by both the description of the crush syndrome in multiple civilian blitz casualties in 1941 and the "proof" of the validity of dialysis in Korea in 1953. However, reflection on wartime statistics gives a more nuanced view of ARF with general applicability.

Retrospective analysis of US military casualties (Burnett, Shapiro et al. 1947; Board for the Study of the Severely Wounded 1952) showed that during the Second World War, 1 in 200 severely wounded soldiers developed ARF, and all of them died (Table 8.4)[229]. Comparable statistics from the wars in Korea and Vietnam reveal mixed

[229] Interestingly, equivalent British reviews of WW II experience (Wiles, P. (1944). "Analysis of battle casualties admitted to Middle East hospitals April 1, 1942, to March 31, 1943." Ibid.: 523-525, Porritt, A. E. (1945). Summary of Surgical Results (Forward Units). London, War Office, Porritt, A. E., R. K.

progress. Dialysis was introduced into the US Army in Korea (Smith, Post et al. 1955; Teschan, Post et al. 1955; Teschan 1965; Teschan 1992; Teschan 1993), and whilst this contributed to the reduced mortality in severe ARF, so also did other developments such as the general availability of antibiotics.

	Ratio ARF : Severely Wounded	ARF Mortality
WW II	1:200	>90%
Korean War	1:400	~70%
Vietnam War	1:600	~50%

Table 8.4 Incidence and Mortality of Wartime ARF

Despite huge investment, including a hospital ship formatted as a renal unit (Lordon and Burton 1972; Lordon 1973) stationed off the Mekong delta, the mortality of dialysed severe ARF in Vietnam remained above 50% (Whelton and Donadio 1969; Whelton 1973; Stone and Knepshield 1974). That the application of the full panoply of 'modern' medicine, including intensive dialysis, could not rescue more than half of these previously fit young men (the average age of GIs was 19 years) led to the acceptance (Fischer 1974) that the prognosis of ARF was determined by the severity of the underlying condition, of which ARF was but a significant complication. The acknowledgement of the priority of the patient's intrinsic problem(s) was subsequently confirmed in civilian practice. In turn, this encouraged debate on futility in the treatment of some critically ill patients and exploration of the possibility of risk-profiling ARF, but not necessarily in any changes in practice.

The American military experience did, however, provide evidence of the value of early and aggressive resuscitation of the severely injured in preventing the subsequent development of ARF. The circulatory, but not the renal, effects of shock had been intensively studied by the Allies in WW I (Anon 1918; Fraser and Cowell 1918; Anon 1919; Moffat, Hamilton et al. 1985; Benison, Barger et al. 1991), and further characterised in the interwar years (Moon 1938; Moon 1942; Moon 1944) before the

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Debenham, et al. (1945). "B.L.A. surgery." Brit Med J **2**: 377-382, Grant, R. T. and E. B. Reeve (1951). Observations on the general effects of injury in man with special reference to wound shock. London, HMSO, Cope, Z., Ed. (1953). History of the Second World War. Medical Series. Surgery. London, HMSO.) make little or no mention of ARF, although Porritt makes a general comment on the inevitable fatality of anuria; seemingly the condition made no 'official' impact other than on individual observers (Darmady, E. M., A. H. M. Siddons, et al. (1944). "Traumatic uraemia." Lancet **244**: 809-812.)

resumption of global conflict stimulated further research in WW II (McDowall 1940; Dunphy 1941; Blalock and Duncan 1942; Moon 1944; McMichael 1945; Beecher, Simeone et al. 1947). These later enquiries, both clinical and experimental, differed by focusing on the newly prominent interest in the acute renal effects of traumatic shock (Belsey 1942; Bywaters 1942; Darmady, Siddons et al. 1944; Lauson, Bradley et al. 1944; Corcoran and Page 1945; Burnett, Shapiro et al. 1947; Burnett, Shapiro et al. 1947; Corcoran and Page 1947; Darmady 1947; Mallory 1947; Moon 1947; Darmady 1948; van Slyke 1948; Simeone, Mallory et al. 1950; Moon 1953). This academic work coincided with the greater availability of stored blood and blood products such as plasma, and an increasingly sophisticated distribution system (Starr 1999). The result was the demonstration of the need for implementation of early aggressive fluid resuscitation and surgical intervention (Janeway 1941; Dick 1944), both of which were progressively refined in Korea and Vietnam (Artz, Howard et al. 1955; Balch, Meroney et al. 1955; Rush, Teschan et al. 1958).The consequence of the change in both practice and the system for battle casualties (for example, the MASH advanced hospitals in Korea (Marble 2012)) resulted in a significant reduction in both the immediate mortality of and the development of ARF in the severely wounded. The benefits of sophisticated resuscitation practice were reinforced in successive Israeli conflicts (Iaina, Reisin et al. 1975; Barsoum, Rihan et al. 1980; Michaelson, Taitelman et al. 1984; Ron, Taitelman et al. 1984) and directly transferred to civilian emergency medicine (Anon 1959; Better and Stein 1990; Slater and Mullins 1998).

From the earliest description of the crush syndrome at Messina (Colmers 1909), earthquakes have been a major cause of multiple casualties with ARF (Collins and Burzstein 1991; Noji 1992) and the finding of the value of aggressive fluid resuscitation from the wartime studies have been repeatedly confirmed following natural disasters worldwide. A recent development is intervention by American and European medical teams, fully equipped even with mobile dialysis facilities, in the aftermath of the Armenian and Turkish earthquakes. This philanthropic impulse raises practical and administrative problems, questions about cost-effectiveness, and even political difficulties (the equipment of the British team was impounded by the Soviet authorities *en route* to Armenia). Evidence again showed that early vigorous resuscitation prevents ARF and is the most effective intervention, but often environmental and economic circumstances preclude this.

The large numbers and relative uniformity of traumatic ARF have made the condition attractive for intervention studies from the WW II (Burnett, Shapiro et al. 1947) trials of alkali infusions to early ("prophylactic") haemodialysis (Silva, Pomeroy et al. 1964; Champion, Sacco et al. 1974; Conger 1975) or CVVH (Gettings, Reynolds et al. 1999; Bauer, Marzi et al. 2001). None of these trials have shown outcome benefit over and above that of effective resuscitation and adequate dialysis. Whether in war (Fischer 1974) or peace (Sipkins and Kjellstrand 1981; Guly and Turney 1990; Morris, Mucha et al. 1991; Ostric, Radovic et al. 1996; Radovic, Ostric et al. 1996; Vivino, Antonelli et al. 1998; Antonelli, Moreno et al. 1999) it became apparent that the outcome of the development of ARF was determined by the site and severity of the injuries, the age of the patients (Finelli, Jonsson et al. 1989; Guly and Turney 1990) and by the development of multiorgan failure (Kennedy, Luke et al. 1963; Faist, Baue et al. 1983; Tran, Cuesta et al. 1994; Saadia and Lipman 1996). This added to the accumulating evidence that ARF is but part of multiple organ dysfunction and its outcome is determined by the underlying condition and the patient's age. Further, the severity and age of patients have increased over time, largely because these now survive long enough to develop ARF because of the 'success' of immediate emergency care.

ARF resulting from trauma has had a central role in the understanding of ARF, largely because its association with dramatic events focuses attention and because the large numbers of victims in wartime[230] and with natural disasters allows doctors scope for intervention, often portrayed as dramatic results. Clearly trauma may result in many adverse events: muscle necrosis, internal or external bleeding, ruptured viscera, penetrating foreign objects, sepsis and the combination of these will vary considerably. The paradigm of the crush syndrome (Abassi, Hoffman et al. 1998) therefore applies in only a minority: the cause of ARF has become yet more complicated. In most Western countries, with the possible exception of the USA, trauma has become a minor cause of ARF, thanks largely to a reduction in incidence of severe injuries due to safety legislation and the relative scarcity of violent crime, and also to the quality of initial emergency care.

[230] This has not been true since Vietnam because of the changing face of conflict, with relatively fewer casualties. For example, only a single case of ARF occurred in British forces in the first Gulf War, and that was a soldier run over by a truck at base camp. It must also be remembered that the military are vulnerable to non-traumatic ARF, for example due to infectious disease, and that this has muddled some of the war-related writings (Lucke, B. (1946). "Lower nephron nephrosis." Milit Surg **99**: 371-396.)

8.10 Direct comparisons between decades

The qualitative evidence that the pattern of patients with ARF had changed over time first received quantitative support in a study comparing specific cohorts from the Leeds series (Turney 1990), in which an attempt was made to answer the recurring question: Why the persistently high mortality in ARF? Medical and surgical patients with sepsis who were dialysed for ARF in 1960-9 and 1980-9 were compared using a standard severity of illness scoring system on the day of the first nephrological consultation (Table 8.5). This showed that the patients in the 1980s were significantly older and sicker, and a much higher proportion required ventilation. The very high (72.5%) mortality in those patients with severe combined renal and respiratory failure was the major cause of the lower survival in the later decade. Statistical evidence of increasing severity of illness as time progressed has been confirmed in a comparison of ICU patients with ARF in the 1980s and 1990s at Guy's Hospital (Abbs and Cameron 1998) and the Mayo Clinic (McCarthy 1996), between the late 1970s and 1980s in Vienna (Druml, Lax et al. 1994), and in unselected ARF patients between 1988 and 2002 in the USA (Waikar, Curhan et al. 2006).

The inescapable conclusion must be that at least between 1950 and 2000 patients with ARF became older and the severity of their disease worsened. The change in severity was determined by both the burden of coexisting disease and the associated acute multisystem organ failure. ARF by the 21st century had become very different from the condition confronting the early proponents of renal replacement therapy.

	1960 – 69		1980 – 89
n	119		124
Deaths	61		78
Survival	48.7%	ns	36.6%
Mean Age	50.9y (7 - 81)	p<0.0001	63.1y (8 - 87)
Ventilated	1.7%	p<0.0001	41.1% (72.5% mortality)
Median APACHE II Score	32 (22 - 45)	p<0.0001	35 (25 – 49)

Table 8.5 Comparison of Leeds ARF Patients, 1960-9 & 1980-9

(Turney 1990)

8.11 Summary

Medicine underwent considerable change in the latter half of the 20th century. This metamorphosis was not limited to the introduction of, and growing dependence on, biotechnology but was also characterised by a reshaping of public and professional attitudes and behaviours. Renal medicine sought to establish its identity in this changing landscape, its character becoming identified with its most visible technology. This technology had relied for its establishment on a disorder also formulated in the post-war period. The specialty, technology and disorder proved not to be determinedly coinstantaneous in their evolution but instead demonstrated a lack of synchronicity. Modulation of one element fed back to the others, sometimes inducing a stepwise mutation and at other times almost imperceptible qualification.

The understanding of the nature of ARF had to be reconsidered as both it and its circumstances mutated. From this rethinking flowed change in practice and ownership, each in turn forcing reconceptualisation of the condition. In its mature modern framing, formulated mid-century, ARF could be understood as a distinct entity. Each individual case might be thought of as having an orderly sequence of cause, more or less constant manifestation, treatment, and outcome. By the end of the century, in most cases a definite antecedent could not be clearly identified, the natural history of the kidney dysfunction had become increasingly uncertain and the outcome unpredictable because each was dependent on contingent circumstance and not primarily determined by the course and complications of the renal failure alone. The post-modern concept of ARF was more diffuse, more disorganised. Acute kidney injury had come to be understood not as a self-contained entity but rather as an amplifier of the detrimental effects of many complications coinciding in biologically vulnerable individuals.

It has been argued in this chapter that the most obvious changes were in the nature of ARF, which had by the end of the century become radically different from the clinical scenario originally confronting those practitioners interested in applying technology to renal problems. Indeed, the similarities between ARF in 1950 and in 2000 were limited to abnormal biochemical measurements and their treatment by some variant of the kidney machine. In virtually every other respect the differences in patients and clinical presentation were notable. This change has been recognised by the coining of and increasing use of the phrase ‘acute kidney injury’ as a noncommittal term encompassing all degrees of renal dysfunction in any setting. Yet the recognition by the profession of

the changing nature of ARF was slow and, despite increasing endeavour, the response has been regarded as inadequate.

The candidate medical and social forces determining the shifting identity of ARF have been reviewed. The conclusion has been that ageing patients with coincident disease are more vulnerable to the stresses imposed by biomedical intervention, which becomes manifest as organ failure. Drugs and procedures may carry adverse potentially nephrotoxic risks. The technical ability to provide medical support at the extremity of existence carries a price: prolongation of life of the failing subject renders them liable to accumulating organ dysfunction. In all these respects, and more, ARF is emblematic of late-20th century medicine and has been offered as a totemic condition reflecting the positive and negative aspects of medical 'progress'. ARF was there at the beginning of the biotechnological 'revolution' in medicine and, with its treatment, gradually changed as the pattern of modern medicine played out.

9. SUMMARY and CONCLUSIONS

"…a conclusion, shewing from various causes why the execution has not been equal to what the author promised to himself and to the public."

James Boswell. *Life of Samuel Johnson.* (1791)

9.1 Summary

An attempt has been made to trace the intertwined histories of a condition, its technology, and the medical specialism involved with them. Although these themes are often considered to be emblematic of the technological medicine of the late 20th century, each had a prior history which shaped their eventual configuration. None was static, each changing under the influence of external circumstances and each in turn reshaping the others in a continuous iterative process.

Chapters 1 – 3 situate the founding of nephrology, the invention of dialysis and the conceptualisation of ARF in relation to more general historical literature. Not only may the separation of the confluent themes seem arbitrary but so also is the order in which they are presented. Although nephrology did not appear as a definitive subcategory of medicine until many years later, the science and practice of kidney disorders does allow consideration of the professional framework in which dialysis came to be established. The wider idea of the process of specialisation allows consideration of the investment in, and structural arrangements for, post-war technological medicine, without which there would have been little call for dialysis and its attendants. Chapter 1 not only considers the post-war economic, attitudinal and scientific milieu in which the treatment of renal failure arose but also allows the introduction of other nephrology-specific technologies which had equally crucial, albeit apparently low-key, significance for the definition of ARF, establishment of dialysis and the building of the specialty. As the literature on nephrology is rather sparse, comparison is made with other specialties. Reasoning by analogy shows that the post-war formulation of the specialty of nephrology has many commonalities with cardiology and some with intensive care, the latter having increasing relevance to the later 20th century story of renal medicine. It is, however, argued that the post-war arrangements within medicine differed elementally from whatever activities might be invoked as antecedents of presently construed specialties. Post-war specialist activity was organ-specific and procedure-defined, this dependence on technology fuelling the dissociation from general medicine. Specialties became hermeneutic entities not only in practice but also in the language of their increasingly esoteric knowledge-base, driven by generous investment in biomedical science. This cultural emphasis on science produced, in some jurisdictions, a divide between academics and practitioners. The latter

came to use commercially-determined tools which more often than not used nonmedical science and technology.

This disconnect between science and technology was apparent in the invention of dialysis, as described in Chapter 2. Although the scientific rationale for dialysis has an identifiable lineage stretching back to the early 19th century, as does the science of its target medical condition, none of this was directly relevant to the assembling of available components into functioning dialysis machines. The science was invoked retrospectively as an explanation of the how and why of the observed effects of the apparatus. Dialysis invention is a prime example of the imaginative bringing together of potentially useful parts into a working assemblage that might help to ameliorate a specific clinical challenge. Dialysis invention was ingenious, but science it most certainly was not.

In common with some other medical innovations, for example cardiac pacemakers with which comparisons are made, the unrefined prototypical dialysis machines attracted little positive support. They were difficult to use and potentially dangerous and appeared to fill no recognised therapeutic lacuna. They simply did not work, or at least not well enough, for the original target problem: chronic irreversible renal failure (ESRD). Despite the enthusiastic promotion by a few isolated individuals, dialysis appeared not to meet a need felt by most clinicians. At the same time, the surge in funding for biomedical science was encouraging established opinion-formers into academic activities divorced from the messy world of the engineering of machines. Additionally, and perhaps more fundamentally, dialysis can now be seen as mould-breaking: for the first time it was possible for a mechanical device to replace the function of an entire organ system. This conceptual leap contradicted the centuries-old way of practising medicine and understanding disease. In this regard, dialysis may be thought of as the sentinel of late 20th century technological medicine. The innovativeness of this machine attracted the attention of some practitioners and of the public. Post-war optimism, especially in the USA, had encouraged the feeling that the application of science, by which was usually meant new machines, would solve most if not all illness.

More or less concurrently with the invention of dialysis, attention focused on a condition which, if not exactly new, had certainly newly gained prominence. Acute renal failure, because of its cardinal feature of potential recoverability, proved empirically to be the condition for which dialysis, as then configured, was best suited. Temporary support by means of the machine might buy enough time for some patients, who would otherwise die, to start the process of natural recovery. Thus it could be claimed that an admittedly somewhat

unusual but invariably fatal condition could be 'cured' by the new technology. A disorder and a device had, as it were, found each other to mutual advantage.

The gradual adoption of dialysis occurred in an atmosphere of individual and institutional enthusiasm for 'modern' technology. By concentrating their efforts on patients with recoverable ARF, including high profile use during the Korean War, the proponents built a case for the continuing use of dialysis. They resolved the conflict with those who advocated a more conservative regimen-based therapy by incorporating the valuable elements of the physiological approach to metabolic derangements into the total management of ARF, which for them included dialysis.

The construction of the concept of ARF is considered in the context of published works on the framing of disease in Chapter 3. As with other conditions, physicians needed a formula to allow them to act, think and communicate. ARF came to be defined by collecting and comparing case-reports and adding pathological and laboratory analyses which were agreed to be diagnostic. If the definition arrived at by c.1950 is retrospectively applied to past publications, a long history of ARF can be discerned. From this it could be argued that the understanding of what became called ARF reflected the thinking and practice of succeeding generations of physicians. From being something of a medical curiosity which was thought to be a cause-specific complication, ARF became redefined as a thoroughly modern affair: a sequel of protean social and medical crises substantiated by the (dys-)function of an organ which could only be particularised in the modern laboratory. By extending the history of ARF backwards from its wider recognition in the 1940s, it can be demonstrated that ARF is an indicator of changing medical practice and hazards. This story has greater impact when the shifting nature of ARF is reconsidered in Chapter 8.

The middle section (Chapters 4 – 6) considers the introduction and adoption of dialysis in Britain in the late 1950s and early 1960s. Appropriately, the focus is on Leeds which acted as the catalyst for this process. Chapter 4 sets the post-war scene by considering not only the general economic and political situation but also the few centres showing an interest in the kidney. These actors have been portrayed as resistant to change and obstructive to the introduction of dialysis. Evidence, including personal testimony, suggests a more nuanced interpretation as physicians sought to cope with a changing situation by applying what they saw as best practice under difficult circumstances. Opinions became entrenched and were successfully challenged by a rising generation of technically-minded acolytes of the new way of delivering medical care. The neophytes did not throw over the old ways of doing things, but rather assimilated those bits they liked as a foundation for their autodidactic

fashioning of a newly empowered specialty, incorporating elements from surgery, medicine and the new technology.

The focus becomes narrower in Chapter 5, which describes the build-up to the start of the continuous period of dialysis in Britain. That this should have happened in a northern industrial city requires some explanation. Leeds General Infirmary was a large, wealthy, semi-autonomous teaching hospital. Its Governors and staff, together with the population of Leeds, professed a strong feeling of proud ownership of the institution, which regarded itself as a key player in the intellectual and civic life of the city. Despite nationalisation a few years previously, such provincial teaching hospitals saw themselves as somewhat apart from and superior to the rest of the NHS. The Board of Governors retained the influence and money to continue what they took to be their traditional role: to act as enablers and supporters of the work of the Consultant staff. The Faculty of Consultants in effect determined policy and the proposal from one of its most respected and influential members to acquire a kidney machine (for which support from the MRC had been negotiated) fitted perfectly with the ambitions of the institution.

It would not have been possible for the participants in the early dialyses at Leeds in 1956 to know whether the adventure that they had embarked upon would be successful or whether, as had happened at the Hammersmith Hospital in 1946, it would wither away because of perceived difficulties and, perhaps, lack of interest. As Chapter 6 recounts, the project proved almost too successful: the demand for treatment produced a workload that at times threatened to overwhelm the staff and facilities. The involvement of the MRC ensured that Leeds, unlike the other centres which gradually followed its example, recorded and publicised the results of their work. These results exceeded reasonable expectation, most dramatically in the survival figures for obstetric ARF. The Leeds unit, for that is what it became through its evolving pattern of practice, not only demonstrated the value of dialysis for the increasing numbers of patients with ARF, but also by developing a total management plan provided a bench mark for succeeding centres.

The situation was not problem-free: new medical challenges arose, relations with the MRC became strained, and a sizeable and influential segment of the profession remained unconvinced of the worth of dialysis. The attitudes of the latter forced the technocratic practitioners to coalesce, and Leeds was instrumental in the formation of registries for dialysis and transplantation which, because of the paucity of participants, were necessarily international in outlook and membership. The heyday of the Leeds unit was probably during the 1950s and 60s, during which time it was the reference centre for ARF and for

transplantation, in which it lead the world for a time. This focus meant that Leeds was reluctant to espouse the burgeoning activity in dialysis for end-stage chronic renal failure.

The refocus of the attention of the growing number of nephrologists towards ESRD had consequences relevant to the last part of this work, which considers the history of ARF and its technology in the final quarter of the 20th century. Newly recognised medical problems and deficiencies in the dialysis procedure enforced refinements and developments, made possible by the entry of industry into what became a huge medical market. Academics, previously suspicious of the scientific worth of the maintenance of life by dialysis, became increasingly involved and identified needs requiring technical solutions. In one specific, but very important, respect technology commercially developed for dialysis for ESRD had a significant impact not only on the treatment of ARF, but also on how it was viewed. For reasons discussed in Chapter 7, dialyser membranes, which act as the interface between the patient and the machine, underwent radical reconfiguration. Understandings and techniques imported from the chemical and textile industries allowed membranes to be designed so that the performance of dialysis was completely altered. Unintentionally, and perhaps serendipitously, these membranes could be used to develop a completely new form of dialysis applicable only to ARF. These continuous dialysis systems proved very acceptable for the management of a new and growing medical challenge: ARF arising in the intensive care unit. The commercial promotion of continuous systems and their enthusiastic uptake by both nephrologists and intensivists had unintended consequences. Not only did ARF become viewed differently, but also the ownership of the condition became contentious.

Chapter 8 is an attempt to measure and explain the changing frame of ARF in the latter part of the 20th century. The rationale is not only that ARF is the defining trope of the present work, but also that the condition as variously understood is emblematic of modern technomedicine. Over the period of interest, what is called ARF changed from a disorder defined by clinical observation supported by laboratory investigation to what in many instances was a biochemical perturbation, the consequences of which had been elucidated by statistical analysis. From a relatively infrequent event it had become a major health issue. From a discrete clinical event in predominantly younger patients it had become part of the abundance of problems besetting the older machine-dependent critically ill person in ICU. The potential causes of acute renal dysfunction had multiplied despite the virtual disappearance of the precipitants challenging the mid-century practitioners. Technological innovations had made it easier to treat and made the treatment more widely available. And yet, treated ARF continued to carry a high mortality, the suspicion even being that the

likelihood of death or failure of recovery of renal function had worsened as time progressed. Increasing investment of huge effort and expenditure in technological life-support had, seemingly perversely, resulted in diminishing returns. This paradox alone justifies the study of the history of ARF and its technology.

The final chapter attempts to explain the observed events by dissecting out changes in patient-related factors such as demography and epidemiology, the effect of changes in medical and surgical practice, the effects of changing definitions, and more subtle but probably more relevant aspects such as the changing impact of sepsis. These complex and intellectually-challenging questions, which appear to go to the heart of modern medicine, seem to defy clear solutions. By tracing the history of definable categories such as obstetric or traumatic ARF, it can be shown that the spectrum and outcome of ARF have indeed changed and that the reasons for this are social and/or largely from outside nephrology.

ARF was framed as a medical condition which was defined and controlled by doctors. Nevertheless it has always been a bellwether of social circumstance: for example as a consequence of global conflict, illegal abortions, inadequate safety legislation, insufficient or too adventurous medical care; its pattern reflects socioeconomic status. As currently configured it raises ethical, medical and financial questions and also challenges the very premise of modern technomedicine.

9.2 ARF as Metaphor: A Concluding Argument

The persistent motif of this work is that ARF is both the practical thread connecting the specialty of nephrology and its identifying technology as well as a conceptual abstraction of modern technomedicine. These concluding remarks attempt to bring together the contexts and consequences of the condition by considering the shifting framing of the disorder, the sufferers, and how and by whom it was diagnosed and treated. That is to say, in as much as there is a definable condition why did it become recognised, by whom, and how did the changes in the condition itself and its circumstances embody changes in a wider context.

For consistency, the term ARF has been used throughout, despite the fact that the same or similar conditions have been given diverse appellations at different times. This inconsistent terminology depicts two cardinal features of ARF:

- ARF is not a ‘disease’ as conventionally imagined: it has neither a unitary causality nor a consistent symptomatic definition;
- ARF is not defined of itself but rather by a shifting conjunction of clinical, scientific and social contexts. It is therefore a symptom complex reflecting current medical understandings.

If ARF should be seen as a chimera constructed from available pointers variably considered to be important, then reflection on its drifting diagnostic threshold casts light on changing medical thoughts. For many years ARF (not then so called) was perceived as a rare complication of severe specific events and so carried the name of the precipitating catastrophe as though it was peculiar to that situation. ARF was defined until at least the late 1940s by the way of medical thinking often called Parisian: symptoms (in this case reduced or absent urine output) associated with post-mortem histological appearances. However, the histology of renal disease was poorly described and the tubular damage characteristic of established ARF did not fit comfortably with the then understanding of renal anatomy and physiology, and premortem histology was rarely obtainable. So diagnosis devolved to merely the absence of normal urine volume, an ostensibly insignificant problem in those few who may have survived a clinical disaster for long enough to develop what would later be called ARF. If treatment of the precipitating cause is ineffective then the victim dies quickly of the primary problem; if resuscitation is sufficient to stave off the immediate consequences then the patient might survive long enough to lose urine output. However, this would probably have been seen as merely one among many signs of impending death. Thus the detailed Allied investigation of shock during World War I did not remark on any renal aspect, whereas by the end of the century circulatory collapse was routinely effectively treated and the development of any subsequent ARF was given primacy in the diagnostic categorisation and management of the critically ill. It was not until after the rediscovery of the crush syndrome that ARF began to have an independent identity. But even Bywaters was initially more concerned with the compression injury to muscles than with ARF, which appeared to be but one of many complications of a specific type of injury.

Quite quickly, reports accumulated of cases with the same signs and morbid appearances following events as disparate as obstetric disasters or tropical fevers. At the same time, improvements in the initial care of, for example, the wounded resulted in mortality being delayed long enough for ARF to become a significant clinical issue. By the end of World War II ARF had become a discrete entity, independent of cause, defined by clinical signs and a unique pathological picture. Increased medical scrutiny led to the appearance that it was no longer a rare event; changing medical practice ensured that its frequency did actually increase. Scattered among the reports were instances in which the fatal outcome was not inevitable: after a period of severe illness, patients regained urine output and eventually recovered. So by say 1945 ARF had moved from an ill-defined medical curiosity to a tightly described entity which, moreover, carried the possibility of recovery, no matter how remote.

Focused medical attention had moved ARF from a relatively unconsidered symptom to an apparently intact entity defined by the metabolic response to specific kidney injury, independent of cause or subject.

Practitioners felt impelled by a named disorder with a less than hopeless prognosis, to contemplate specific treatment. The first such response was firmly embedded in the practice and knowledge of the time, that is to say it was an adaptation of the longstanding principles of regimen by the application of physiological knowledge of renal metabolism. This treatment was entirely compatible with traditional physicianly practice and referral hospitals, by adopting it, could begin to accumulate experience in the increasingly frequent, and increasingly frequently recognised, cases of ARF. Such centres achieved some success arising from expertise and attention to detail as well as, perhaps, the opportunity to treat milder cases which were now recognised earlier as knowledge spread and outlook appeared less pessimistic. Although published evidence showed the dietary regime to be an improvement on no treatment, the impression remained for some, especially among those dealing with traumatic or surgical cases, that more needed to be done for the most severely affected. This desire for more active intervention appealed primarily to young surgeons, who not only tended to see the worst cases but also who are usually characterised as ‘doers’ rather than physician ‘watchers and waiters’. It was from this quarter, outside the then professional mainstream, that dialysis was offered as an additional treatment for suitable cases.

There was in the first post-war decade a conjuncture of a newly defined disorder, a potential technological treatment, and some in a new generation of doctors receptive to the concept that technology could beneficially be applied to medical treatment. Dialysis, offered to a generally sceptical profession as a mechanical replacement of organ function, was notably unsuccessful when first tried. It could at best provide only temporary amelioration of the biochemical mayhem of advanced renal failure, and then only with some difficulty. Dialysis failed its intended patient population but was found empirically to benefit those whose kidneys had the potential to recover. Dialysis became reserved for those with ARF. By restricting treatment to this specific clientele, the few centres employing dialysis were able to demonstrate its utility. Without this directed effort, even the hesitant acceptance of the procedure would surely have been further curtailed. This selective treatment demanded precise diagnosis of ARF and accumulating experience demonstrated improved results if dialysis was applied before the patient had become terminal. Diagnosis could no longer be predicated on signs and symptoms which lacked precision, but now required repeated estimations of blood chemistry and, in problematic cases, renal biopsy. Although authors

such as Peitzman and Cameron suggest that the need to diagnose ARF was the driver of the uptake of biopsy, in reality it was required to exclude what was *not* ARF, and therefore perceived as not suitable for treatment. Accepting that their device was adequate for ARF alone, practitioners used biopsy to confirm a diagnosis in cases not self-evidently recovering ARF. The information so obtained became a justification for the withdrawal or withholding of 'active' treatment.

The routinisation of laboratory measurement meant that the diagnostic criteria for ARF started to move away from the subject's experienced complaints towards a laboratory-centric way of regarding renal dysfunction. Thus diminishing urinary output, whilst retaining some influence in signalling a potential problem, changed from being a cardinal symptom to insignificance as biochemistry gained ascendancy as the sole indicator of ARF. It no longer mattered what the kidneys looked like or indeed what the patient was experiencing, all that counted were the numbers. The abundance of oft-repeated biochemical estimations were fertile material for statistical manipulation. This showed that in any given clinical situation, chemical perturbations that had previously been thought to be therapeutically unimportant turned out to carry (statistical) significance in terms of outcome. This resulted in a skirmish in the age-old clinical confusion between consequence and subsequence. A rise in serum creatinine could be, like a reduced urine output had once been, regarded as a symptom of a more systemic problem. But the contrary view was taken: because of the primacy of biochemical measurement, changes were taken to be diagnostic of a fundamental renal problem that could of itself determine prognosis. It even gained a new name: acute kidney injury, with connotations foregrounding the role of the kidneys and indicating something bad just falling short of 'failure'.

The enumeration of medicine, characteristic of the end of the 20th century, has proved an exceptionally efficient method for converting information into resource, and for devising large-scale approaches to disease. But so authoritative are numbers, so apparently irrefutable the knowledge they dispense, that numeracy has all but eliminated the sense of the worth of disease-as-story: of medicine that is self-made, felt, experienced. The rigorous exactitude of numbers celebrates precision, and suppresses touch, feel and provisionality. The incommensurance of personal illnesses and the subjective humanity of the clinical interaction have become marginalised by digital certainty. The paradox may be that the compelling verisimilitude of numerical collations obscures the questions to which they purport to be the answers.

The progressive lowering of the diagnostic threshold for ARF gained relevance from the hugely increased availability and ease of use of dialysis. Industrial development had made dialysis machines sophisticated self-governing 'monitors' and, further, had resulted in systems for continuous indefinite dialysis. No longer was there a need to prioritise patients by some system of perceived severity or need. Anybody with abnormal blood tests could (and indeed should) be treated, on the assumption that correction or even normalisation of the biochemistry would improve the eventual outcome. The machines do not, of course, affect whatever underlying disease process is in train. Diagnosis and treatment had become a self-fulfilling circular argument, predicated on a presumed prognosis. The wish to utilise available technology to the maximum had in effect driven a change in diagnostic certainty from a discrete clinical entity to an amorphous numerical abnormality.

The causes from which ARF is consequent have changed as a result of social and medical events, and have led to a change in the pattern, frequency and prognosis of ARF itself. If one considers the 1950s and 1960s in the UK and elsewhere in the Western world, the majority of patients had causes that later became preventable as a result of legislation or improved medical practice. As these causes which predominantly affected younger adults declined, ARF cases came to be older patients carrying significant comorbidity exacerbated by increasingly adventurous medical and surgical intervention. Presumably in the early days of dialysis (from the records of which the data on causes are derived) patient selection excluded those with chronic disease or malignancy who either did not receive primary treatment (if any were available) on the basis of age or prognosis and/or if they did and later developed ARF, dialysis was withheld for the same reasons. However, this speculation appears not to fully explain the observed epidemiological shift which meant that by the last two decades of the century ARF was not only much more frequent but was also the province of older patients with renal dysfunction acquired in hospital, not in the community. The liberalisation of the diagnosis of ARF is but a partial explanation and does not explain the parallel rise in 'sepsis', which is also a complication of modern high-tech medicine.

Perhaps the clearest indication that ARF is a disease of modernity is provided by its epidemiology in developing economies such as India or Brazil. There, the rural poor continue to experience the 'old' pattern of causation: poisons, environmental hazards, abortion and obstetric complications, trauma, etc. In contrast, the increasingly affluent expanding urban population now mirror Europe and America. With the adoption of a westernised way of life has come a western burden of ills. If ARF is taken as an emblem of modern illness, then what is remarkable is that the velocity of socioeconomic change has been so closely matched by

the change in the epidemiology of ARF. Community-acquired ARF has markedly declined as a proportion in all urbanised communities, having been replaced by ‘new’ problems: older persons with multiple pathologies undergoing modern medical procedures and treatments and so repeating the pattern set in the west some 20 or 30 years previously.

If the ideal medical scenario is diagnosis directing treatment and so informing prognosis, then ARF rather fails this test. The mutating diagnostic criteria have been, at least in part, influenced by the available technical intervention, which is not the traditional sequence. Paradoxically, the prognosis, with or without dialysis, has worsened as the frequency has increased and as more resources have been committed to it. This has been ascribed to the changing demography, but deeper excavation of the available data suggests that this explanation is partial. It became necessary to diagnose ARF when possible treatment became available, which did improve its prognosis. But the commitment of more treatment did not result in further improvement but rather in a worsening of prognosis.

ARF displays a shifting dynamic pattern which includes the label, which has itself dissolved into an unreadable ‘black box’. Initially it was suggested that ARF is semiotic of modern technomedicine. Perhaps, in fact, it has become emblematic of the post-modern not easily definable interrelationship of science, society and medical practice.

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