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The Ulster Medical Journal

NEPHROLOGY TODAY

Symposium held on 7 September 1984
to mark the 25th anniversary of
the founding of the Renal Unit, Belfast City Hospital

Supplement Editors

MARY G McGEOWN, CBE, DSc (Hon), MD, PhD, FRCP
CC DOHERTY, MD, MRCP

THE ULSTER MEDICAL JOURNAL

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The Ulster Medical Journal, Volume 54, Supplement, p. S4, August 1985.

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Formerly Professor of Medicine, Queen's University of Belfast. Lately Director of MRC Clinical Research Centre.

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Department of Renal Medicine, Manchester Royal Infirmary.

500 Years of the Nephrotic Syndrome: 1484-1984.
Professor J. S. Cameron, BSc, MD, FRCP.
Guy's Hospital Medical School.

High Blood Pressure — A Problem of Renal Volume Homeostasis.
Professor Jan Brod, MD, FRCP.
Director, Department of Internal Medicine, Medical School, Hanover.

Renal Bone Disease.
Dr. J. A. Kanis, FRCP.
Department of Human Metabolism and Clinical Biochemistry, The University of Sheffield.

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Jervis Street Hospital, Dublin.

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Consultant Urologist, Belfast City Hospital.

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Chairman, Registration Committee, EDTA, St. Thomas' Hospital, London.

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Professor of Transplantation Immunology, University of Heidelberg.

Chairman **Mr. R. A. Donaldson, BSc, FRCS.**
Transplant Surgeon and Consultant Urologist, Belfast City Hospital.

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Chief, Section of Transplantation, Director of Surgical Research, Mount Carmel Mercy Hospital, Detroit, Michigan.

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Mr. R. W. G. Johnson, MS, FRCS.
Consultant Transplant Surgeon, Manchester Royal Infirmary, Manchester.

Second Northern Ireland Kidney Research Fund Lecture

Chairmen **Mr. Robert Moffett,** Chairman, Northern Ireland Kidney Research Fund and **Dr. M. G. McGeown.**

Haemodialysis: 25 Years of Progress.
Professor D. N. S. Kerr, MD, FRCP.
Dean, Royal Postgraduate Medical School, Hammersmith Hospital, London.

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THE ULSTER MEDICAL SOCIETY

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This covers one volume (two numbers) of the Journal.

The Ulster Medical Journal, Volume 54, Supplement, pp. S1 – S2, August 1985.

Introduction

Due to the foresight of Professor Graham Bull and Mr John Megaw, the Renal Unit was established in the Belfast City Hospital in 1959 to provide treatment for patients with acute reversible kidney failure. Plans were made to alter part of Ward 9 to provide a dialysis room, a preparation area cum office and two cubicles for patients, but the artificial kidney, a Kolff twin coil kidney, arrived long before the premises were ready. After a trial run in the Department of Surgery on a dog made anuric by ligation of the ureters, I planned to see the equipment in use at the Royal Air Force Renal Unit in Halton. However, before this could be arranged, in June 1959 an 80-year-old man with severe uraemia due to prostatism was admitted, and the late Mr Megaw persuaded me to treat him. The artificial kidney was taken to an operating theatre in Ava 2, and despite my complete lack of experience with the equipment a very satisfactory improvement in the patient's biochemistry was achieved. From then on we were in business, and for the next nine months the artificial kidney treatment became a travelling service, being set up near the patient where there was any sort of plumbing. The patients suffered from post-obstetric renal failure, trauma, incompatible blood transfusion etc, and some still survive.

In the summer of 1960 the premises in Ward 9 of the City Hospital were ready and patients were brought there for treatment. The first technician emigrated to Canada and Jack Lyness joined the service, and is therefore the second longest serving member of the team. There was no question of a one-in-three rota then: take-in then, as now, was continuous.

The workload rapidly increased: patients with non-reversible renal failure began to be referred, and attempts had to be made to treat them. During the early years the nursing was carried out by whatever nurse could be spared from Ward 9, but things improved after Staff Nurse Kay Maguire, now Nursing Officer, was appointed as the first renal nurse in 1963. There was a close association with the urological surgeons from the beginning. The late Mr Megaw was generous with the loans of his senior registrar over the early years. Mr Joseph Kennedy's association dates from his senior registrar days in 1962. Another early helper was Mr Billy Graham, now consultant surgeon in Craigavon Area Hospital.

From 1965 we began to provide regular haemodialysis for two patients with end-stage renal failure, treating the patients by night with the original equipment which was needed also for treatment of patients suffering from acute reversible renal failure. Over the next few years a small number of patients were sent to St. Mary's Hospital in London or Addenbrooke's Hospital in Cambridge for renal transplants. The success of this 'transplant brokerage' opened the way to setting up transplantation in Belfast in 1968.

A specially designed building, Renal I, was opened in July 1968 to allow transplantation to begin and also provided space for regular dialysis for six patients. On 22nd November 1968, the first kidney transplant was carried out. After a period of anuria due to acute tubular necrosis, the graft functioned well for almost three months, when it was lost from acute irreversible rejection. In 1969 four transplants were performed, all of which succeeded, and three of the grafts are still functioning well sixteen years later, one patient having died of a myocardial infarction with a functioning graft. The dialysis facilities were

increased by provision of a 10-bed unit (Renal II) in 1972. Just after that we suffered a small outbreak of hepatitis B which caused great anxiety, but fortunately it was limited to four patients and no staff were involved.

Both dialysis facilities and transplantation have increased over the past 12 years, and in our best year (1982) 46 transplants were carried out. The need for treatment still exceeds the facilities, and the service is stretched to the utmost and beyond as we try to treat patients with diabetes mellitus and other serious diseases which were formerly considered unsuitable, as well as a few older patients.

The work of the Renal Unit depends on the co-ordinated effort of a team of doctors, nurses and technicians. Inevitably the team has changed over the years and past members are too numerous to list, though Mr Stewart Clarke, Dr Joseph McEvoy and Dr J. C. Hewitt, who were part of the original transplant team, must be mentioned. The work also depends heavily on laboratory services, the radiological department and other hospital services. The expansion of kidney transplantation has been possible only because colleagues in intensive care units have been willing to undertake the extra work involved in obtaining donors.

The support of the Northern Ireland Kidney Research Fund has contributed greatly to the development of the service and it is a pleasure to acknowledge their help.

M.G.McG.

The Ulster Medical Journal, Volume 54, Supplement, p. S3, August 1985.

Obituary

Jan Brod, MD, DSc (Prague), FRCP

Jan Brod, professor of medicine at the Medizinische Hochschule, Hannover, died on February 10, 1985, aged 72.

He qualified in medicine from Charles University, Prague, in 1937, after which he worked in hospitals in Prague and Vienna. After the German occupation of his country he held a French Government research fellowship until the invasion of France, when he joined the Free Czech Army and served in first aid stations. After the collapse of France he joined a Czech field ambulance in Britain, and during this time he worked in Northern Ireland, and was stationed at Moira and Ballykelly. He attended the Physiology Department then headed by Professor Henry Barcroft and developed a friendship which continued when Professor David Greenfield succeeded to the Chair of Physiology. He spent some time in the Department of Medicine during a visit in 1957, when I met him first. This meeting led to an invitation for me to give a lecture on hyperparathyroidism in Prague in 1958, and to a friendship which continued until his death. The paper he delivered at the 25th Anniversary Symposium, typed by himself, was posted only 3 days before he died.

After the war Jan worked as a Rockefeller Foundation fellow with Professor George Pickering in London and Professor Homer Smith in New York, before joining the Institute of Cardiovascular Research in Prague. He was Director of the Institute from 1963 until he left Prague when the Russians occupied Czechoslovakia in 1968. After a short period as Visiting Professor in Mainz, he became Professor of Medicine in Hannover where he remained until he retired in 1981.

Jan was a great man as well as a great medical scientist and clinician and was fluent in eight languages. He had a deep love and knowledge of music and literature. His numerous publications and several books, including the large volume *The Kidney,* remain as testimony to his medical scholarship. The nine symposia on renal topics which he organised in Hannover will be long remembered by all who attended them.

He is survived by his wife Ula and a son who is a medical student in Oxford.

M.G.McG.

The Ulster Medical Journal, Volume 54, Supplement, pp. S5 – S19, August 1985.

Five hundred years of the nephrotic syndrome: 1484-1984

J Stewart Cameron

SUMMARY

The nephrotic syndrome has emerged over several centuries as the consequence of continued profuse proteinuria, arising in turn from a variety of lesions affecting the glomerulus which impair glomerular ability to retain plasma proteins, in particular, albumin. As a syndrome, it has its own complications and requires its own management irrespective of the underlying lesions. Dissection of these by renal biopsy and by clinical investigation reveals a variety of systemic diseases which affect the kidney, but a majority of primary immune-based diseases appear unique to the glomerulus. Whether the lesion called by Müller and Munk 'nephrosis', and now called minimal change disease and focal segmental glomerulosclerosis is one disease or many, is the subject of intense debate at the moment, as is the relationship between two types of lesion. Only a better understanding of their pathogenesis, and of how the glomerulus normally retains plasma protein, will solve this knotty problem.

Although dropsy (oedema) in adults has been known from classical times (for example, to Hippocrates [1]), the distinction between the various causes of oedema in these early texts — nutritional disturbances, cardiac failure, liver and gastrointestinal disease as well as renal disease — is not possible to define. One sage observation made by Hippocrates about the nephrotic syndrome, however, is familiar to many patients and doctors — that 'when bubbles settle on the surface of the urine, it indicates disease of the kidneys and that the complaint will be protracted'.[1] This effect of albuminuria on the surface tension of urine may even be the presenting complaint of some patients, and the date of onset of profuse proteinuria can usually be determined by direct questioning.

However, in children the causes of severe oedema are a little less complicated, and thus I take as the start of studies of the nephrotic syndrome itself the book *Liber de aegritudinibus infantium*[2] (Fig 1) published about 1484 by Cornelius Roelans (or Roelants) of Mecheln in Belgium (1450-1525). He describes 52 diseases of children, of which the fifty-first is 'swelling of the whole body of the child'. It seems almost certain that he is describing nephrotic oedema here, but the short chapter is mainly devoted to a confused account, based on the Galenical theories of humours, of how the swellings might arise; the kidneys are nowhere mentioned. At the end, however, he states: 'Then the child may be cured by a remedy that I found in a certain pamphlet on diseases of children. Take the tops of the elder plant, and danewort, cook in white wine and wrap the child in hot cloths by applying a poultice in whole or in part, and so cure him'. Perhaps a prospective controlled trial is needed here! Roelans also gives homely advice on

Guy's Hospital, London.

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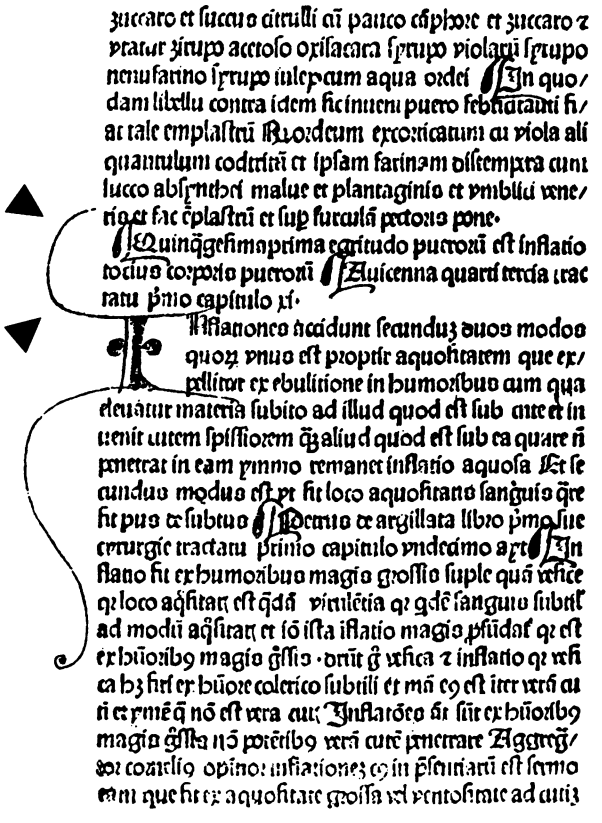

Fig. 1
The page in Cornelius Roelans' *De aegritudinibus infantium* of 1484 which contains perhaps the earliest description of a nephrotic child: 'The fifty-first disease of children is swelling of the whole body of the child'. Reproduced from reference 2.

less abstruse problems of childhood such as teething pains (treat with honey and butter on the gums of the child).

We now leap forward almost 250 years, to a really remarkable early description of the nephrotic syndrome by Theodore Zwinger III of Basel (1658-1724) in his *Paedoiatreia practica* of 1722.[3] This text is known to some historians of paediatrics,[4] but has been completely ignored by nephrologists. His description of the physical signs of the nephrotic syndrome in chapter 119 is quite remarkable, and is worth quoting in full: 'Oedema, generally called hydrops, is a condition involving swelling of the whole body. From head to foot the skin is a pale dirty yellow, the swelling is oedematous and characterised by inflation of the whole periphery with persistent collections of lymph. The swelling is not hard or tense, but such that the print of a finger remains behind. Commonly, thirst is very great, the bowel action not as free as usual, and the urine is scanty because of obstruction and compression of the tubules of the kidney. The breathing is difficult, often accompanied by anxiety because of the compromised function of chest muscles and diaphragm from the swelling of the skin. Besides, there is a continued fever, and soon a strong desire to sleep appears because the brain is overfull with serum; sleep is poor because of disturbance of the "spiritus animalis". Additionally, there may be a dry cough from irritation of the nerves to the lung by the liquid, salty lymph. At the beginning, the swelling may be small, but later it increases steadily if the remedies used do not have their expected effects, so that

legs, abdomen and even the face are blown up with a bluish colour, and one must fear attacks of suffocation. We have seen children of either sex in whom the eyelids were so swollen they could not open their eyes, and also the genitalia were so swollen and full of serum, that they looked almost transparent. In boys, the virile member was so swollen that they could make water only with difficulty'.

Thus in 1722, more than 100 years before Bright, Zwinger described the nephrotic syndrome and placed the seat of the disease firmly in the kidneys! This is all the more remarkable, because at this time Morgagni had of course not published his great classic *De sedibus et causis morborum,*[5] which established the idea that diseases might arise from specific organs. Incidentally, in this latter work one can find one of the first descriptions of the pale, mottled kidneys of the nephrotic patient.

Zwinger did not, however, perform any tests on the urine that we know of, and it was only after proteinuria had been described for the first time in conjunction with oedema by Domenico Cotugno (1736-1820) in his *De ischiade nervosa commentarius* of 1770, that Richard Bright (1789-1858) and others could put together the triad of proteinuria, diseased kidneys and oedema. Despite the fact that other observers in Britain, notably William Wells of St Thomas' Hospital[7] and John Blackall of Exeter,[8] came close, Bright's claim to having described the nephrotic syndrome in all its detail in his classic *Reports of medical cases* of 1827[9] must be sustained, in conjunction with the chemical observations of his lesser-known colleague, John Bostock (1773-1846), chemist and physician of Liverpool. Bostock[10] quantified the urine and serum proteins by methods depending upon specific gravity, noting that the greater the amount in the urine, the less in the blood. This observation was confirmed in 1829 by Robert (later Sir Robert) Christison of Edinburgh (1797-1882),[11] who stated: 'The specific gravity of the serum has always been lowest where the urine was loaded with albumin. It is hence probable that the albuminous secretion of the urine is nothing more than a transudation of serum from the blood'.

Thus, by 1830 the nephrotic syndrome of profuse albuminuria, hypoalbuminaemia and oedema resulting from diseased kidneys leaking protein into the urine was established.

One of the many tasks to which these early workers addressed themselves (and which remains uncompleted to this day) was to establish how the oedema came about. The usual explanation is given in Fig 2, which presupposes that, during the active formation of oedema at least, the circulating plasma volume will be low, and that what are usually called Starling forces will operate less avidly than usual because of lowered oncotic pressure in the plasma. This theory was, however, suggested by a certain J-C Sabatier in Paris as early as 1834:[12] 'The serum of the blood being depleted (of albumin) becomes more fluid, thinner and by this it is able more easily to penetrate the walls of the arterial capillaries. If it is possible to suppose that, following this modification of the blood, venous absorption is less active, one can see how in such cases the effusions in the serous cavities and infiltrations of the tissue may arise'.

The problem of how nephrotic oedema accumulates is still not settled,[13] and Dorhout Mees and his colleagues have repeatedly emphasised their own[13-15] and earlier observations[16, 17] that the plasma volume in stable, untreated adult nephrotics is usually *normal,* or even increased. In contrast, many paediatricians (and rather fewer internists) including ourselves have seen *un*treated patients with

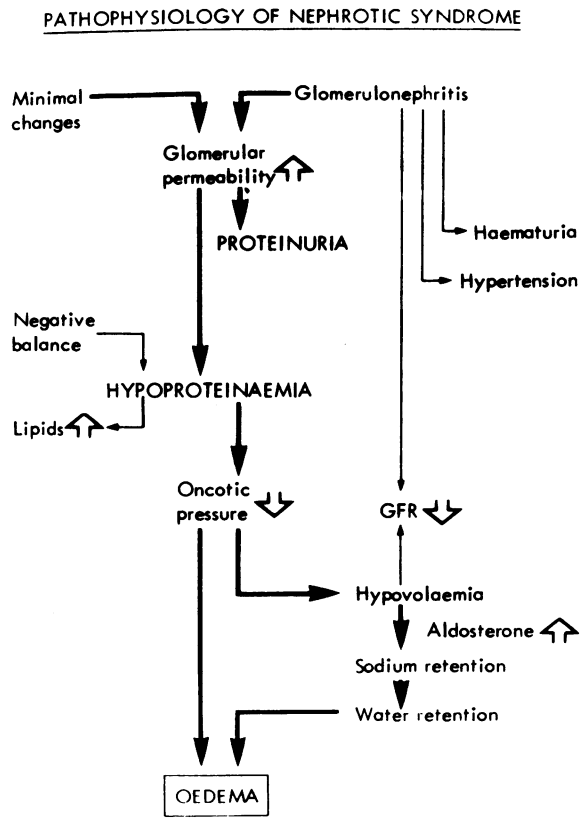

Fig. 2
The usual explanation for the accumulation of nephrotic oedema, which presupposes a reduced plasma volume at least in the phase of active oedema formation (See text).

a nephrotic syndrome, usually with minimal change disease, arrive at hospital already in shock or even in established acute renal failure. Melzer and colleagues[18] pointed out that patients with minimal change disease (who form the great majority of patients with a nephrotic syndrome in childhood) usually have high plasma renins, whilst the levels in most other nephrotic patients are normal.

Thus, it does seem possible to reconcile these disparate observations. Immediately after proteinuria begins, or reaches nephrotic proportions, the plasma albumin falls as a result of both excretion and increased renal catabolism of reabsorbed albumin. The plasma volume contracts, triggering humoral and physical stimuli to the renal tubules which result in more avid retention of sodium, and secondarily of water. Excretion of a water load in nephrotics is reduced in most studies[19] and occasionally true hyponatraemia may be seen as opposed to 'false' or 'dilutional' hyponatraemia dependent on high lipid levels. This retained salt and water is distributed more into the tissues than normally because of the lowered plasma oncotic pressure, but gradually the plasma volume is restored to normal — at the price of an expanded extracellular space, a great increase in total body sodium (which can more than double) and visible oedema. Thus the patient 'purchases' a normal plasma volume in the face of hypoalbuminaemia; but the price is oedema. Equally, if the doctor gives diuretics he will eliminate thia oedema, but the 'price' will be hypovolaemia.

TABLE I

Complications of the nephrotic syndrome

Common:	Infections	1° peritonitis, cellulitis ± septicaemia
	Thrombosis	venous ± embolism arterial
	Hypovolaemia (± diuretics)	circulatory collapse acute renal failure
	Hyperlipidemia	? accelerated atherogenesis*
	Protein depletion	osteoporosis ± stones striae wasting
Uncommon:	Fanconi syndrome*	
	Fe deficiency anaemia	

* particularly in patients with focal segmental glomerulosclerosis.

One of the complications (Table I) from which nephrotic patients may suffer is **acute renal failure.** The cause of this acute renal failure principally seen in nephrotics with minimal change and focal sclerosing lesions,[20, 25] is not known. Diagnosis may be difficult if the patient presents in this state, since the urine will contain not only large amounts of protein but also red and white cell casts and many red blood cells, presumably the result of associated tubular necrosis. Thus, the appearances exactly mimic those of an acute proliferative glomerulonephritis, with or without crescents, and early renal biopsy is necessary to make the diagnosis (see below). To begin with, this complication of acute renal failure was thought always to be associated with hypovolaemic shock and circulatory collapse,[21] and there is little doubt that this accounts for some cases, often accompanied by septicaemia (see below). Another group of nephrotic patients who go into acute renal failure have been given large doses of contrast media, or non-steroidal anti-inflammatory agents,[22, 23] both of which are known to be nephrotoxic. The latter group is of particular interest since the agents (especially fenoprofen) seem able to *induce* a minimal change nephrotic syndrome, with or without an infiltrate, mainly of T-helper cells, in the interstitium.[24] Finally, and most puzzling, is a group of patients who present in acute renal failure without any antecedent circumstances except growing oedema, without any signs of hypovolaemia, and who have minimal changes in their renal biopsy.[25] These patients tend to be older than 50 and relatively resistant to treatment with corticosteroids; they sometimes do not recover renal function and may succumb because of nutritional and other problems associated with persisting torrential proteinuria — despite their oliguria — together with uraemia. We have seen four such patients, of whom only one survived. Lowenstein and others[26] have suggested that a factor in acute renal failure in these nephrotics may be increased renal interstitial pressure from oedema, but no measurements have been made to support or deny this hypothesis.

Another complication that nephrotic patients may suffer is **thrombosis.** It seems strange that Bright and his colleagues, with their large experience of nephrotic

patients, do not comment on this aspect. This is all the more surprising when we realize that many of their patients (including Mary Sallaway, whose case is described in the *Reports of medical cases,* and whose kidney is still in the Gordon Museum at Guy's Hospital) suffered from amyloidosis;[28] we know now that such patients are particularly prone to develop renal venous thrombosis.[29] However, the first descriptions of renal venous thrombosis came from Osborne in Dublin,[30] who made little of the association, which he found by chance at post mortem in a nephrotic middle-aged man without specific symptoms. The first detailed description of renal venous thrombosis was by Bright's great Parisian contemporary, Pierre Rayer (1793-1862), in his encyclopaedic book and atlas on diseases of the kidney, published in 1840.[31] In this he described two cases of renal venous thrombosis in nephrotics: one being of a young prostitute who had acute loin pain and fever in association with the thrombosis.

There is much controversy about the incidence of renal venous thrombosis in nephrotic patients.[27, 32-36] The only point above contention is that it is much commoner in nephrotic patients with membranous nephropathy, an association which remains unexplained; presumably some as yet unstudied aspect of coagulation is more abnormal in such patients (see below). Several authors[32, 34] have shown that, by careful angiography, up to as many as 40% of nephrotic patients with membranous nephropathy may have small, silent renal venous thrombi, and a lower, but still substantial proportion of patients with other forms of glomerular disease underlying their nephrotic syndrome are similarly affected. However, my associates and I, in common with other workers,[35] have been unable to confirm these findings, only 5-10% showing thrombosis. It may be that there are real geographical variations in the incidence of renal venous thrombosis in membranous nephropathy, and hence in the nephrotic syndrome as a whole.

What is not clear either is *what should be done* about symptomless venous thrombosis if it is found. No prospective study has dealt with the question of what happens in such patients who are *not* anticoagulated (as must happen to their symptomless counterparts who do *not* have angiography), and are thus never diagnosed. It is clear that, in the presence of anticoagulation, symptomless renal venous thrombosis is benign, neither renal functional deterioration nor increase in proteinuria being associated with its presence, either at the time of diagnosis[31, 32] or later. Unfortunately, neither ultrasound nor CAT scanning seems able to equal the performance of invasive angiography in making the diagnosis, a procedure not without risk. Thus, few clinicians perform venography in *all* their nephrotic patients unless symptoms indicate;[36] but many will perform it routinely, or have a lower clinical threshold for performance, in nephrotic patients with membranous nephropathy.

Thrombosis as a whole is a danger which stalks the nephrotic patient, and remains a worrying source of morbidity and mortality. What makes it of particular note is that diuretic treatment, presumably by raising the haematocrit and increasing blood viscosity,[37, 38] may *increase* the chances of thrombosis. It has been a cause of death in our own series of adult[77] and childhood[49] nephrotics, and in a recent series of nephrotic children.[39] However, the pattern of thrombosis is different in adults and children.[27] One large survey of European centres[27, 40] found that almost half the children had arterial thrombosis, whereas in the adults the great majority had venous thromboses, although arterial thromboses are also seen.[27] In children, the arterial thromboses affected almost any artery in the body, intracardiac and pulmonary artery thrombosis being remarkably

common[27, 40] and aortic thrombosis recorded.[27] It is worth noting that the only other group of children who suffer similar major vessel thromboses are those with congenital cyanotic heart disease with high haematocrits. Venous thrombosis is remarkably common in nephrotics. At a clinical level in our own series, 11 of 89 adult-onset minimal change patients had deep venous thromboses, associated with obvious pulmonary emboli in seven, whilst only one had an arterial thrombosis (femoral). Doppler ultrasonography, however, reveals that as many as one quarter of adult nephrotics have thrombi in their deep calf veins.[41] Similarly with pulmonary embolism: less than 5% of adult nephrotics overall will have clinically evident emboli, but ventilation/perfusion isotope scanning reveals that about 15% have evidence of pulmonary emboli.[27, 42] This complication is rare, however, in nephrotic children, as it is in children as a whole. Renal venous thrombosis, whether symptomless or evident. is associated with a high incidence of emboli, averaging about one third of cases in 11 published series.[27]

Why do nephrotic patients show this extraordinary tendency to thrombosis? (Table II). There are many abnormalities of circulating haemostatic proteins,[27] both procoagulant and regulator, in the nephrotic syndrome.[27] In general, those of low molecular weight are lost into the urine in excess of synthesis, and so the plasma concentrations fall (factor IX, X, XI, XII, prothrombin, plasminogen, antiplasmin, antithrombin III, protein C, α_1 antitrypsin); whilst, in those of high molecular weight, synthesis exceeds losses, with a rise in plasma concentrations (Factor VIII/von Willebrand factor, fibrinogen, factor V, factor VII, α_2 macroglobulin). It is difficult to judge what effect all these alterations will make in an individual case. There is already present in the plasma a manifold excess of such factors as VIII, V and VII, and whether further increases produce a prethrombotic state is doubtful. Although antithrombins are lost into the urine (antithrombin III, α_1 antitrypsin) α_2 macroglobulin rises, so that the total antithrombin activity is normal or even raised in most nephrotics. Inhibitors of plasmin are essentially the same serine protease inhibitors, with the addition of α_2 antiplasmin, which protein accounts for much of the *in vivo* activity; this is usually reduced in nephrotic patients. Recently, however, Pollak and his associates[43] have implicated both inhibitors of plasminogen activation and antiplasmin in the genesis of thrombosis in nephrotic patients, particularly renal venous thrombosis in those with menbranous nephropathy.

TABLE II

Factors involved in the thrombotic tendency of nephrotic patients

Humoral	Raised factors I, V, VII, VIII
	Raised plasma lipids
Platelets	Hyperaggregability — ? arachidonate↑
Fibrinolysis	Reduced plasminogen
	Antiplasmins
	Loss of antithrombins in urine
Mechanical	Immobility
	Repeated vascular punctures
	Haemoconcentration — viscosity raised
Iatrogenic	Corticosteroids
	Diuretics — worse hypovolaemia

However, it may be that abnormalities of platelet function account for much of the thrombotic tendency in nephrotics.[44] When plasma albumin is reduced, the number of binding sites competing with the platelet cycloxygenase for arachidonic acid is reduced. Thus, more arachidonate is available for thromboxane A_2 synthesis by the platelets, which increases, and *ex vivo* platelets will aggregate supranormally to arachidonate, ADP or collagen, a phenomenon which can be corrected both *in vivo* and *ex vivo* by the addition of albumin.[44] Clinically, the nephrotics at risk of thrombosis are those with a severe reduction in serum albumin to below 20 g/l,[42, 44] and it may be that this hyperaggregability operates through this mechanism. However, our own recent unpublished observations that nephrotic platelets are hyperaggregable to ristocetin, which does not require arachidonate or thromboxane A_2, suggests that this is not the whole story.

The most common complication of the nephrotic syndrome in former times was however infection, which, until the antibiotic era, resulted in early death in the majority of nephrotic children[45, 47] and a considerable number of adults.[48] Even in the present era replete with antibiotics, sepsis is still a problem, accounting for deaths in our own series of children,[49] as well as those of the International Study.[39] The peculiar susceptibility of nephrotic children to infections with encapsulated organisms, in particular *Strep. pneumoniae,* has been noted for many years. This infection seems never to occur in adults, our oldest patient with pneumococcal peritonitis being 21 years of age. It is probable that this peculiar susceptibility is associated with losses of alternative pathway components of the complement system in the urine,[50] although why adults should be protected is not known. Primary peritonitis, usually with septicaemia, is of course the commonest presentation, and a recent analysis of peritonitis shows,[51] as in our own experience, that in children it is still a problem. In Krensky's review of peritonitis over the period 1970-1980,[51] 24 episodes of peritonitis occurred in 19 of 351 nephrotic children: 50% were from *Strep. pneumoniae,* and 25% from *E. coli.*

Another major problem which was a cause of death until the antibiotic era was cellulitis. This can spread with terrifying rapidity in the oedematous tissues of the nephrotic patient, and may arise from splits in the skin occasioned by the swelling. The organism is usually present in the blood stream and can more usually be obtained from the blood than from the local lesion.

The final complication of the nephrotic syndrome that I wish to deal with was heralded by John Blackall in 1811,[8] who noted that the serum of blood drawn from nephrotic patients was milky in appearance; an observation which may well have been made earlier in dropsy, given the popularity of blood-letting in the eighteenth century. Twenty-five years later, Robert Christison established by its solubility in sulphuric ether that this material was indeed fat.[59] We now know[53] that there are complex alterations of lipoproteins in nephrotic patients, with rises in VLDL and LDL cholesterol fractions, although in most patients HDL is normal, being low only in an occasional patient with relentless proteinuria and very low serum albumin; of the subfractions, HDL2 is selectively reduced. In all cases with or without visually evident hypertriglyceridaemia, the total cholesterol is very much elevated in proportion to the reduction in plasma albumin. The reasons for the increased hepatic synthesis of apoprotein, which is responsible, along with urinary losses, for these changes, are poorly understood. Naturally these changes in circulating lipids lead to speculation as to whether nephrotic patients are more susceptible to vascular disease, and in particular myocardial infarction, since

similar changes in the blood fats of control populations are known to be associated with increased mortality from vascular causes. It has proved surprisingly difficult to give an answer to this apparently simple question.[54, 55] From the beginning, it seemed that children and young adults with a nephrotic syndrome and precocious atheroma suffered from relentless nephrotic syndromes, and a number had what we would now recognise as focal segmental glomerulosclerosis (FSGS) lesions.[46, 56, 57] In fact, it emerges from follow-up studies[58] that rather few other patients remain nephrotic for long periods of time — only one-third had a nephrotic syndrome for more than four years in our study. The remainder either lose filtering surface and go into renal failure, with diminishing proteinuria, or remit spontaneously or in response to treatment. It is noticeable that in progressive FSGS with renal failure, profuse proteinuria may persist right into terminal renal failure and even require nephrectomy. Thus, only a tiny proportion of nephrotics are subjected to continuous hyperlipidaemia over many years. Finally, many of these patients have underlying glomerular disorders complicated by hypertension, itself a powerful risk factor in the genesis of vascular damage.

Thus the question is not a simple one. Anecdotally, there is no doubt that some nephrotics suffer thrombosis of their coronary arteries,[59-61] and it is tempting to attribute this as a complication of their nephrotic state as one would any other thrombosis, or as a result of the lipid alterations. Because of small numbers, it has not proved possible to study individual subgroups particularly at risk (for example patients with focal segmental glomerulosclerosis) but overall our large nephrotic population in the South-East of England did *not* show a mortality significantly in excess of a carefully-matched local control population.[58] Other papers on the subject have not made similar comparisons with appropriate controls.[59-61]

Until 1950, our knowledge of the underlying histopathology of the kidney in nephrotic patients was based on those unfortunates coming to post mortem either through renal failure, or through some complication of the condition.[45-48, 62] It was known well before 1900 that a nephrotic syndrome could complicate diabetes, syphilis,[8] treatment with mercury,[8, 30] amyloidosis,[63] and last of all Schönlein-Henoch purpura[64] and systemic lupus.[65] It had been known even earlier that a nephrotic state might complicate post-scarlatinal nephritis,[66] and thus some idea of 'secondary' and 'primary' nephrotic syndromes was established quite early. However, the histology of these 'primary' nephrotic syndromes continued to puzzle workers in the field from 1900 onwards. In general, they could see few changes using the optical microscopy of the period in many of these nephrotics dying of complications, including those suffering from syphilis. Friedrich von Müller of Marburg (1858-1941) made his major (and dubious) contribution to nephrology in 1905[67] by introducing the term 'nephrosis' as an antithesis to 'nephritis', implying a 'degenerative' lesion of the kidney rather than an 'inflammatory' one; this term was popularized by Fritz Munk (1879-1945)[68] who mainly studied syphilitic nephrotic syndromes. The techniques of the period could not distinguish the early changes of membranous nephropathy, almost certainly present in these patients, from normality; and it was not until 1932 that ET Bell,[69] using newer stains, described severe membranous nephropathy. Workers of the period were unable to accept the possibility of a functional defect in the glomerulus without changes visible on optical microscopy, and thus the idea of 'pure nephrosis' (minimal change disease, as it would now be called) as a tubular lesion became current. About the same time, Henry Christian[48] and Louis Leiter[45] in the United States pointed out the similarities of primary and secondary

forms of severe proteinuric disease with oedema, and introduced the terms 'syndrome of nephrosis', or 'nephrotic syndrome', to emphasise the relationship, which gradually achieved popularity.[70]

We recognise now, following the introduction of percutaneous needle renal biopsy to the study of glomerular disease in the early 1950s by Poul Iverson and Claus Brun in Denmark,[71] and Robert Kark and Bob Muehrcke (then a medical student) in the United States,[72] that as well as the many different clinical circumstances associated with the nephrotic syndrome, a variety of different types of histopathology may underly it,[73, 74] thus making the dissection by the technique of needle biopsy a major feature of the management, at least in adults. The pattern of underlying histopathology for an unselected British population of nephrotics is shown in Fig 3. This is based on a personal series of more than 500 patients with onset over the age of 15, and for 200 children biopsied up to 1970, when we ceased to biopsy every nephrotic child.

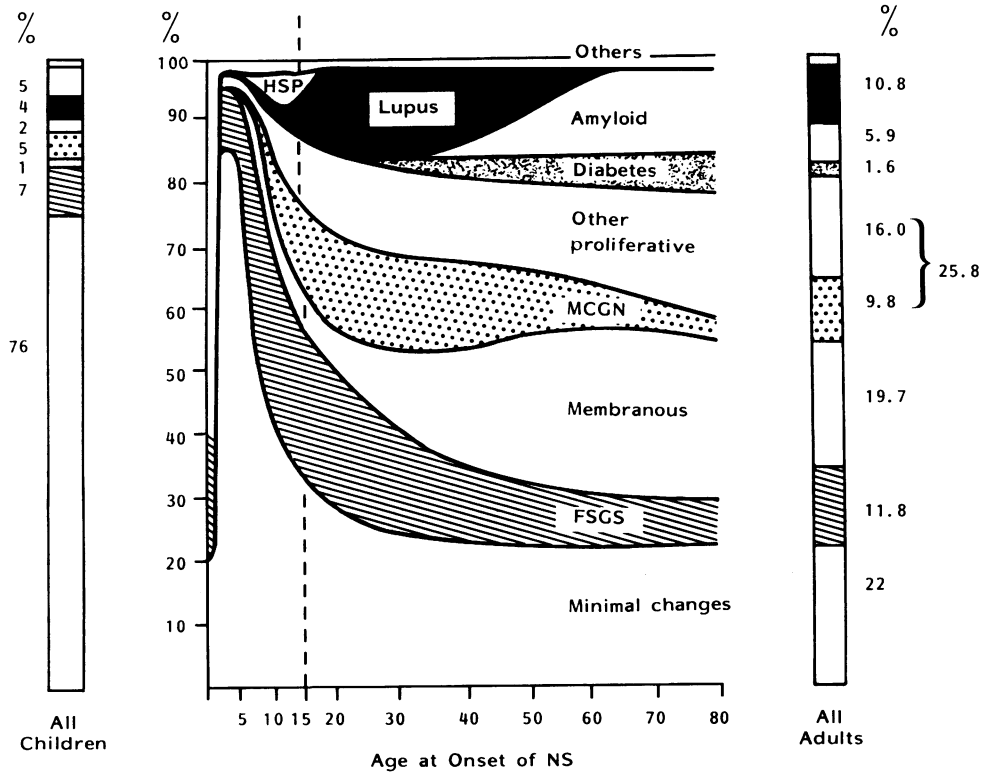

Fig. 3. The underlying glomerular histological appearances found in a series of over 700 nephrotic children and adults seen at Guy's Hospital 1963-1984. The 506 adult biopsies were taken during the whole of this period; the 200 children were all biopsied before 1970, at a time when (as is still our policy in adult nephrotics) *all* children with a nephrotic syndrome were subjected to renal biopsy.

(HSP = Henoch-Schönlein purpura; FSGS = focal segmental glomerulosclerosis; MCGN = mesangio-capillary glomerulonephritis; 'other proliferative' includes predominantly crescentic (extracapillary) forms, IgA- and IgM-associated nephropathy and other mesangial proliferative glomerulonephritides, and focal proliferative glomerulonephritis. 'Others' includes all other forms of glomerular disease not included in the above categories, e.g. the congenital (Finnish) nephrotic syndrome in infants, microscopic polyarteritis and paraproteinaemia in adults, etc.)

The reasons for this decision are evident in the diagram: under the age of 6 or so, the overwhelming number of children show the minimal change lesions of 'lipoid nephrosis' and almost all are responsive to corticosteroids, losing their proteinuria within at most 4 weeks' treatment. A further 25% of those with focal segmental glomerulosclerosis will also lose proteinuria. Thus, it is justified to give almost all young nephrotic children corticosteroids, provided their urine does not contain persistent haematuria with casts. Then in the minority, with no response by at most 4 weeks, a biopsy can be done at this point.

Recently, it has been suggested that a similar policy be adopted for adult nephrotic patients,[75, 76] on the grounds that the extra information gained from this invasive procedure does not justify the risk. The calculations used involve some rather uncertain data or assumptions, but the idea falls down on two other accounts. First, how long in an *adult* with minimal change disease must corticosteroids be given to achieve a good chance of remission? An analysis of our own adult series of patients with minimal change nephrotic syndrome, shortly to be published,[77] shows that adults take much longer to respond to steroids than children: treatment for at least 16 weeks, not 4 weeks, would be necessary to identify the non-responders — who would be some 70% of the total, not 10%. The risks of a longer course such as this to the majority who would not benefit almost certainly exceeds the dangers of renal biopsy, especially in older patients. That this difference between adults and children is not simply the result of using relatively lower doses of corticosteroids in the adults is suggested by the observation that their response to an identical dose of cyclophosphamide on a bodyweight basis (3 mg/kg/ideal weight for height for 8 weeks) is similarly retarded.

Also, there are very few clinical pointers which will indicate either an early response to treatment with corticosteroids, or a good prognosis in the long run (Table III). Surprisingly, renal function at presentation is little or no guide to the degree of underlying irreversible renal damage, since the haemodynamic events of the nephrotic syndrome override the effects of the underlying type of glomerular disease. Obviously the age at onset, as indicated in Figure 3, gives some clue as to what the likely cause may be. Hypertension also is of little help in

TABLE III

Prognostic factors in the nephrotic syndrome

Observation	Effect on prognosis
At onset:	
Persistent haematuria	Often bad
Hypertension	Sometimes bad
Diminished renal function	Useless
Persistent hypocomplementaemia	Usually bad
During subsequent course:	
Loss of proteinuria to corticosteroids	Good
Spontaneous remission of proteinuria	Good
Failure to lose proteinuria on steroids	Sometimes bad
Persisting nephrotic syndrome > 2 years	Usually bad

adults with nephrotic syndromes; patients with minimal change disease are hypertensive surprisingly often at onset,[13-15] which remits with the proteinuria; and we have made the same observations in some childhood nephrotics; presumably this is the result of volume contraction and renin secretion. A low serum complement is of use principally because of its association with mesangiocapillary glomerulonephritis (MCGN), which in general has a poor prognosis. However, above all, it is those nephrotics with persistent microscopic haematuria as well as profuse proteinuria who in general do badly, since this is a characteristic of most of the progressive forms of glomerular damage. In the longer term, persistence of the proteinuria at nephrotic levels is a poor prognostic sign. Long-term studies in our unit show that, in most patients who will ultimately heal, the proteinuria rarely remains in the nephrotic range more than a year or two. Conversely, the serum creatinine is almost always raised permanently in those with progressive disease after only 2-4 years of evolution. Essentially all patients who lose their proteinuria maintain their renal function, unless hypertension has developed and is inadequately treated.

Another interesting observation we have made recently[49, 77, 78] is that the frequency and rate of relapses in minimal change nephritis patients declines steadily with increasing age at onset of the disease. In children. all those who ran very long-term relapsing courses had an onset less than six years of age, and the average number of relapses declined steadily from 1-15 years of age. Amongst adults, the same gradient with age is evident: although as high a proportion of adults have at least one relapse as in childhood (about 70%), overall the total number of relapses is much less; that is, fewer adults become frequent relapsers. This is particularly noticeable in the older patients: over 60 years of age, relapses are rare, although the initial nephrotic episode in these old patients may be devastating and some may die in the acute phase.

For a much more extended account of the history of the nephrotic syndrome, the reader is referred to Chapters 1 and 2, by JS Cameron and RJ Glassock, and RM Kark respectively, in the forthcoming book *The nephrotic syndrome,* edited by JS Cameron and RJ Glassock (New York: Marcel Dekker), now in preparation.

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Volume homeostasis, renal function and hypertension

Jan Brod †

SUMMARY

A generalised vasoconstriction, for almost a century believed to be the basis of all types of human hypertension, was disproved by recent haemodynamic studies. In our investigation of hypertension in chronic parenchymatous non-uraemic, non-anaemic renal disease, we have established that the earliest haemodynamic abnormality in subjects, of whom over 90% later develop high blood pressure, has actually started while their blood pressure is still normal. This consists of hypervolaemia and a high cardiac output (hyperkinesis) with tissue hyperperfusion. Hypervolaemia is due to a failure of these still normotensive patients to excrete isotonic saline as readily as subjects with completely normal kidneys.

The chronic hypervolaemia in these subjects leads to a release of the natriuretic factor which depresses the Na^+-K^+-ATPase in the cell membranes and which is responsible for an increase in sodium (and calcium) content of the vascular smooth muscle cells, diminishing their compliance and thus raising the vascular resistance together with the thickening of the vascular wall of the originally hyperperfused vessels. With the disappearance of the vascular adjustment to the increased cardiac output, the blood pressure rises and the 'pressure diuresis' restores the circulating blood volume (and the renal homeostatic efficiency) to normal. With a further rise of the peripheral vascular resistance the cardiac output falls. At this late stage of renal hypertension renin may play a contributory role.

Thus, the primary abnormality in the chain of events leading eventually to hypertension is a renal inability to maintain a proper balance between sodium intake and output. This suggested pathophysiological mechanism is probably valid in every kind of human hypertension where a reason for such a disturbance is present.

INTRODUCTION

In his *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme,* published 125 years ago, Claude Bernard[1] deduced with a clear foresight that a constancy of the 'milieu interne' is a prerequisite of the 'freedom and independent existence' of the body. Fifty years later, Starling[2] concluded that both the osmolality and the volume of the extracellular fluid belong to the constants regulated by the body within narrow limits. Whilst the former is homeostatically controlled by the hypothalmic osmoreceptors and the posterior pituitary lobe, and whilst the organism is protected against larger losses of the extracellular fluid which endanger the body by a hypovolaemic shock to the

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renin-angiotensin-aldosterone system, protection against isotonic volume expansion appears to be less alert.

Almost 50 years ago Smith[3] showed that ingestion of 1000 ml 1% salt solution in man will produce only a minimal (if any) diuretic response. In this respect, dogs respond faster, the renal reaction consisting of a rise of renal blood flow and glomerular filtration rate (GFR).[4]

TWO TYPES OF HAEMODYNAMIC AND DIURETIC RESPONSE TO ISOTONIC VOLUME EXPANSION IN MAN.

Studying the haemodynamic, diuretic and humoral response to an intravenous saline infusion amounting to 2% body weight (bw), administered within 20 to 30 minutes to 61 fasting normotensive subjects recumbent at the time of the investigation, we have observed two types of haemodynamic behaviour.[5] In 31 the blood pressure remained completely unaffected by the isotonic fluid expansion (group A), whereas in 30 the blood pressure rose by some 14 mm Hg mean pressure (group B). Group B subjects were some 5 years older than those in group A but there was no difference between them in weight, height or sex distribution (Table). Group A consisted of 24 healthy subjects: four had a slight selective proteinuria below 1 g/24 hours without any other sign of a renal disease; in one, latent polycystic kidney disease without any restriction of renal function was discovered in the course of family screening and two gave a history of past border-line hypertension though blood pressure had been within the normal range without any drugs for several months. The mean 24 h glomerular filtration rate (GFR) of the whole group was 133 ± SEM 11 ml/min and the difference between the mean GFR during day-time and night amounted to 28 ± SEM 7 ml/min. Of the 30 subjects in group B, 29 had definite signs of a renal disease (glomerulonephritis bioptically confirmed in 13, interstitial nephropathy in 7, polycystic kidney disease in 2, mild vascular nephrosclerosis with a normal blood pressure at the time of the study in 7). Their mean GFR was also within the normal range (126 ± 11 ml/min), but the difference between the day-time and nocturnal mean was reduced to 11 ± 2, 5 ml/min, which was significantly less than in the previous group.

The cumulative water and salt excretion during the 8 hours following the infusion amounted to 64% and 63% of the ingested load in group A and to 47% and 46% in group B (Fig 1). This points to a restriction of the volume homeostatic

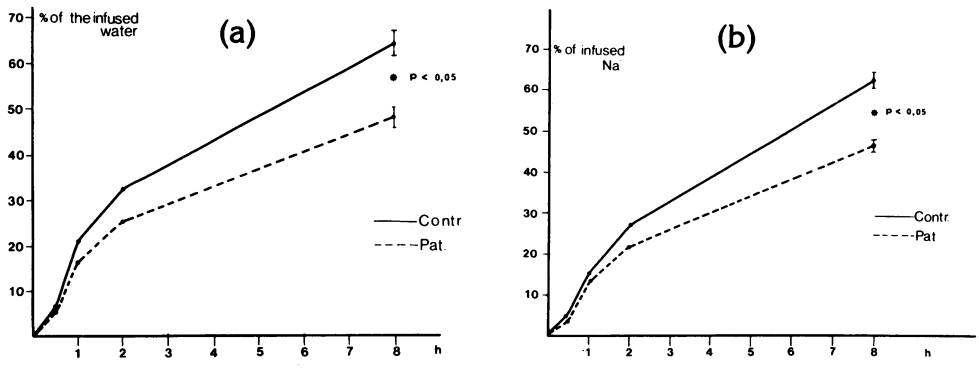

Fig. 1. Cumulative excretion of (a) water and (b) sodium following an infusion of 20 ml/kg isotonic saline in 20-30 minutes to 18 perfectly healthy subjects (group A, Contr.). and to 10 subjects with minor renal pathology (group B — Pat.).

TABLE

Clinical and laboratory data on subjects in groups A and B

	AGE	WEIGHT	HEIGHT	SEX m/f	BLOOD PRESSURE		MEAN BLOOD PRESSURE		BLOOD VOLUME	HAEMATOCRIT		PLASMA VOLUME		GFR	
	years	kg	cm		mmHg		mmHg		ml/kg b.w.			ml/kg		ml/min	
					before	end of infusion	before	end of infusion		before	end of infusion	before	end of infusion	mean	span day/night
GROUP A															
	27.2	68.5	175.9	20/11	137/81	135/79	100.0	98.3	75.0	38.7	35.0	46.3	53.9	132.7	28.1
SEM	± 1.25	± 1.78	± 1.63		± 3.5/3.0	± 3.6/3.1	± 2.9	± 3.2	± 10.9			± 7.8	± 9.0	± 11.4	± 7.1
31					n.s.		n.s.			<0.01		<0.01			
GROUP B															
	32.3	72.2	173.5	17/10	143/81	156/95	104.2	112.4	85.6	39.8	36.1	48.9	59.4	126.4	11.0
SEM	± 1.67	± 2.35	± 1.87		± 4.6/3.6	± 5.9/3.7	± 3.7	± 4.1	± 13.3			± 7.9	± 10.2	± 10.7	± 2.5
30					<0.01		<0.01			<0.01		<0.01			
A B	<0.02	n.s.	n.s.	n.s.	n.s.	s <0.01 d <0.02	n.s.	<0.02	<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	<0.05

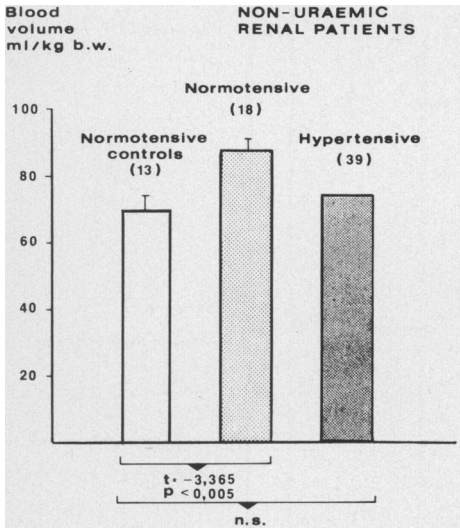

Fig. 2. Resting circulating blood volume in subjects of group A (normal) and group B (normotensive renal patients) and in hypertensive patients stage I to II WHO.

efficiency in group B with a possible trend to volume expansion. This was actually found.[5] The circulating basic blood volume (before the start of the infusion) in group A was 72 ± 5 ml/kg, and in group B 86 ± 13 ml/kg and the difference was statistically significant (Fig 2).

From the dilution of the plasma proteins at the time of the infusion it was possible to calculate that some 30% of the infused load was still within the vascular bed augmenting in both groups the circulating plasma volume. In 34 subjects (13 from group A, 21 from group B) in whom we have carried out detailed haemodynamic studies,[6, 7, 8] this raised the central venous pressure by some 125% and the cardiac output (CO) by some 25% in both groups (Fig 3). However, in group A there was a substantial drop of the total peripheral vascular resistance (TPR) from a control value of 1380 dyn.cm^{-5} sec to less than 1000 dyn.cm^{-5} sec at the end of the infusion whereas its fall was irregular and much smaller in group B. The forearm vascular resistance in group B was from the start significantly above that of group A and the forearm venous compliance rose markedly in group A, whilst it remained unchanged or fell in group B. Thus the two groups differed in their reaction of the peripheral vascular bed to the volume expansion: while it adjusted fully to the volume load in group A, it failed to adjust in group B.

Atrial natriuretic factor. The mechanism of this peripheral circulatory adjustment to the volume expansion in healthy subjects (group A) has been until recently only partially understood. Pressure-receptors in the heart atria were suspected and thought to mediate a reflex peripheral vasodilatation, slowing of the heart and a slight respiratory inhibition.[9, 10, 11] Recently, however, it has been possible to extract a group of polypeptides with a strong natriuretic and vasodilating action from the atria of rats (atrial natriuretic factor — ANF, atriopeptin). They appear to be produced or stored in the large secretory granula of the atrial cells (cardiocytes)[12] and are released on fluid expansion into the blood leaving the heart. Their presence has been established by radio-immunoassay, and their diuretic action is abolished by a specific antibody.[13-18] No proof of their existence in man has so far been reported, but, if confirmed, they would provide an adequate explanation of the augmented vascular compliance to an increased cardiac output and blood volume. The prompt rise of urine flow in rats contrasts with the slow onset of the diuresis on volume expansion in man and will require further study.

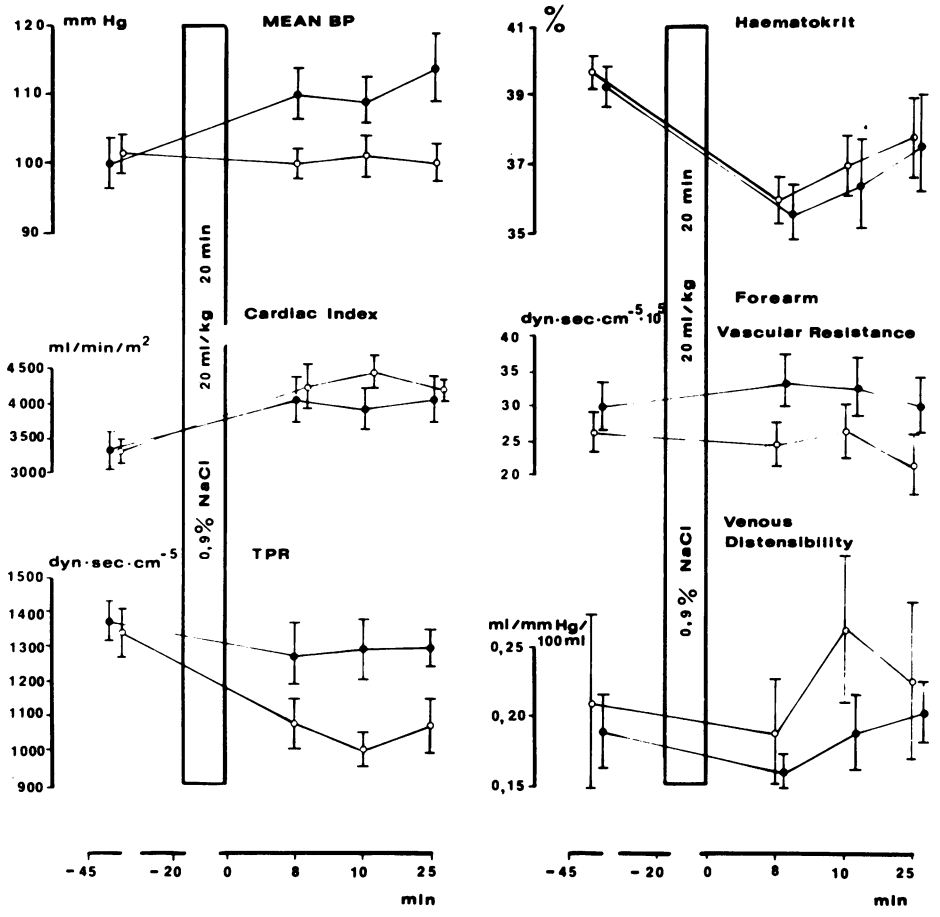

Fig. 3. Central and peripheral haemodynamic changes after volume expansion in 13 subjects in group A (open circles) and 21 subjects in group B (closed circles).[6]

Na^+-K^+-cell-membrane-pump-inhibiting natriuretic factor. This is of a so far uncertain biochemical nature, and is released on volume expansion from the hypothalamus in the neighbourhood of the anterior part of the third ventricle. It suppresses in an ouabain-like fashion the efficiency of the Na^+-K^+-pump in the cell membrane of the erythrocytes, leucocytes, vascular smooth muscle, heart muscle and possibly many other systems in the body with the result that these cells become depleted of potassium and richer in sodium.[19-22] In the kidney this leads to a diminished sodium reabsorption and an increased natriuresis. It has been postulated that the diminished membrane potential permits more calcium to enter the cells and that this is the reason for their diminished compliance, increased contractility and irritability.[23] This latter point is still controversial but the recent findings of an increased cytoplasmic calcium in the thrombocytes of spontaneously hypertensive rats and in essential hypertensive patients[24] lend support to this possibility.

Activation of this principle in normotensive men after volume expansion of some 3-4 litres of isotonic saline administered over several hours will lead to the

appearance of natriuretic activity.[25, 26] We have tested this question in our group A subjects before and after volume expansion as described above, studying the ^{42}K-uptake from an isotonic saline solution with added $^{42}K^+$ with and without ouabain (the pump activity being the difference in ^{42}K transport between the two). The intra-erythrocyte electrolyte concentration was also estimated.[27] In healthy subjects the $^{42}K^+$ transport into the erythrocytes amounted to 1.34 ± 0.28 mmol.h^{-1}.1^{-1} RBC and the intra-erythrocyte sodium concentration to 6.14 ± 1.86 mmol.l^{-1} RBC. At the end of the infusion in these healthy subjects the activity of the pump was unchanged (Fig 4). The meaning of this finding will become evident after the changes in group B have been discussed. The plasma renin activity (PRA) fell to insignificant levels after the infusion in all subjects.

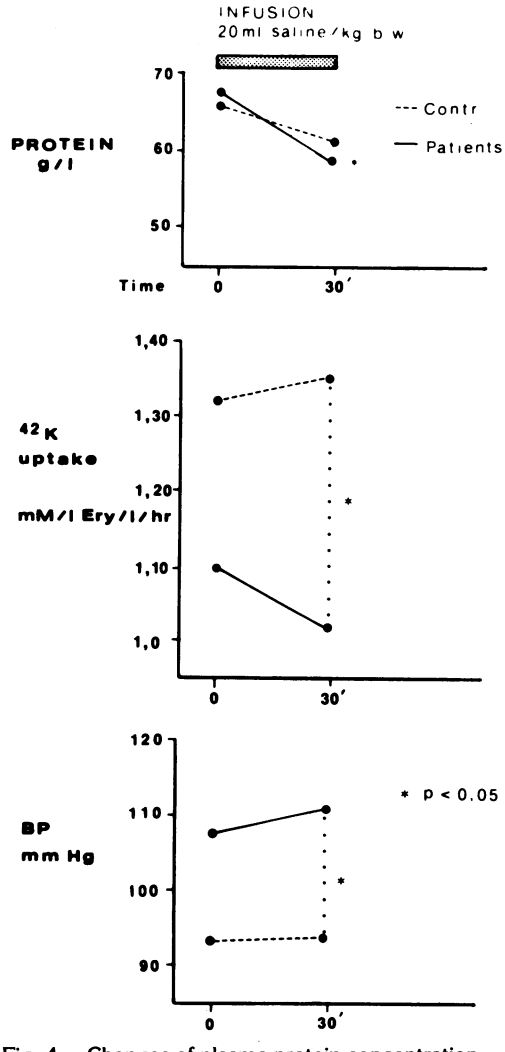

Fig. 4. Changes of plasma protein concentration, ^{42}K-uptake by the erythrocytes and blood pressure after volume expansion as in Fig 1 in 18 subjects of group A and 10 of group B.[5]

Isotonic volume expansion with a rise of blood pressure (group B).

The situation is substantially different in this group where the volume expansion starts from a volume of blood *a priori* raised. These patients had already before the beginning of the infusion, as a consequence of the hypervolaemia, suppressed their Na^+-K^+-pump to 1.10 ± 0.2 mmol K^+.h^{-1}.1^{-1} RBC. The intra-erythrocyte sodium concentration did not change substantially after the 15-minute infusion, but the intra-erythrocyte potassium concentration was slightly reduced in group B. These changes probably reflect an enhanced activity of the natriuretic principle of hypothalamic origin.[22]

Hyperkinetic circulation in the normotensive renal patients.

In a larger series of 97 patients (Fig 5) with chronic parenchymatous renal disease (glomerulonephritis, interstitial nephropathy, polycystic kidney disease) without anaemia (Hb above 12.5 g/dl) and with an adequate renal function (mean 24 hr GFR over 50 ml/min), there were 32 with a normal blood pressure (BP = 145/95 mm Hg, mean BP 115 mm Hg). More than one-third of these had a cardiac index exceeding by more than 2 SD⌀ the mean of the healthy controls (3.09 ± 0.26 l/m^2/min). In spite of their very high cardiac

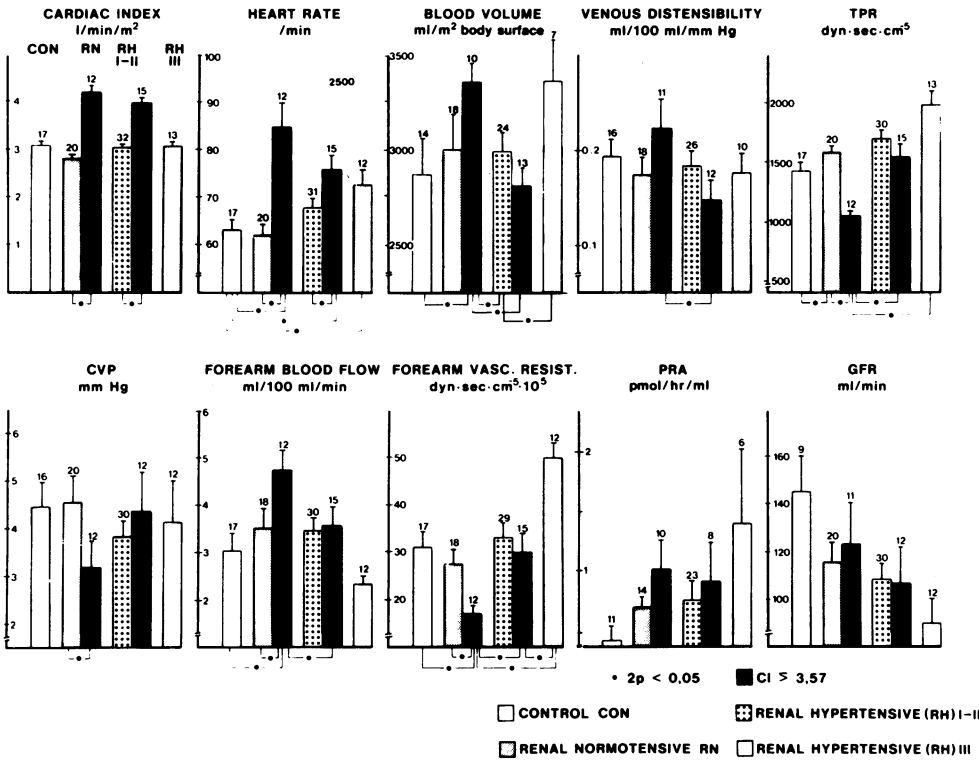

Fig. 5. Central and peripheral haemodynamic pattern, PRA and GFR in healthy controls (CON), in normotensive renal patients (RN) and in patients with chronic non-uraemic parenchymatous renal disease (RH I-II, RH-III) (WHO). The black columns indicate hyperkinetic subjects (cardiac index above 1.57 l/m^2 body surface). CVP = central venous pressure.

output (the mean cardiac index of these hyperkinetic subjects amounted to 4.18 $l/m^2/min$) these patients remained normotensive because both their TPR and the vascular resistance in their forearm were markedly diminished and adjusted to their high cardiac output. This resulted in an over-perfusion of tissues, evident from the strongly increased forearm blood flow (5 ml/100 ml forearm/min compared with 3 ml in controls). The venous compliance was also enhanced, adjusted for the very high circulating blood volume of 93 ml/kg. Fig 6 shows that 92% of these subjects developed hypertension in the course of the following 2 to 6 years, compared with the 45% of the normokinetic ones.[8]

DEVELOPMENT OF RENAL HYPERTENSION

This transition is obviously ushered in by the loss of peripheral vascular adjustment: the TPR is now back at its control value, so is the forearm vascular resistance. When this happens, the kidney is perfused under an increased pressure, and possibly, with the contribution of the Na^+-K^+- inhibiting natriuretic principle whose activity has already been raised by the hypervolaemia of the normotensive stage (Fig 7),[27] regains its volume-homeostatic efficiency at a higher blood pressure level. This explains why in the past this 'transient variable' of hypervolaemia, present only in the normotensive renal patients, remained

undetected, as hypertensive renal patients were compared only with normotensive healthy controls.[28]

Renin and angiotensin can hardly be held responsible for this loss of peripheral adjustability, PRA being the same or even slightly lower (1.22 ng/ml/h) in these than in the normotensive renal patients (1.32 ng/ml/h) where the adjustability of the vessels had been fully preserved (Fig 5)[8] The occupation of the angiotensin vascular receptors by the inactive angiotensin antagonist saralasin did not reduce the blood pressure of these early renal hypertensive subjects (Fig 8).[29]

Further development of hypertension to stage III (WHO) now becomes entirely a function of the peripheral

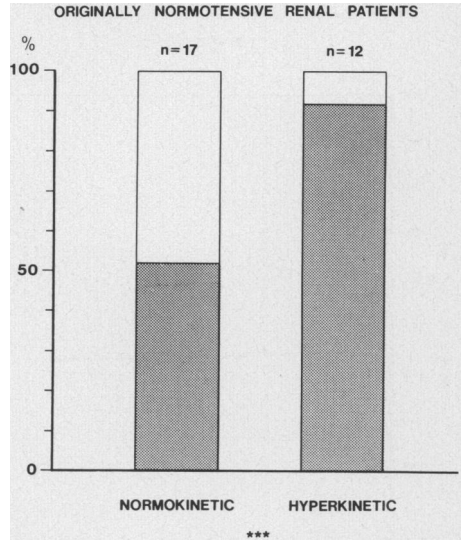

Fig. 6. Later incidence of hypertension in previously normotensive renal patients.

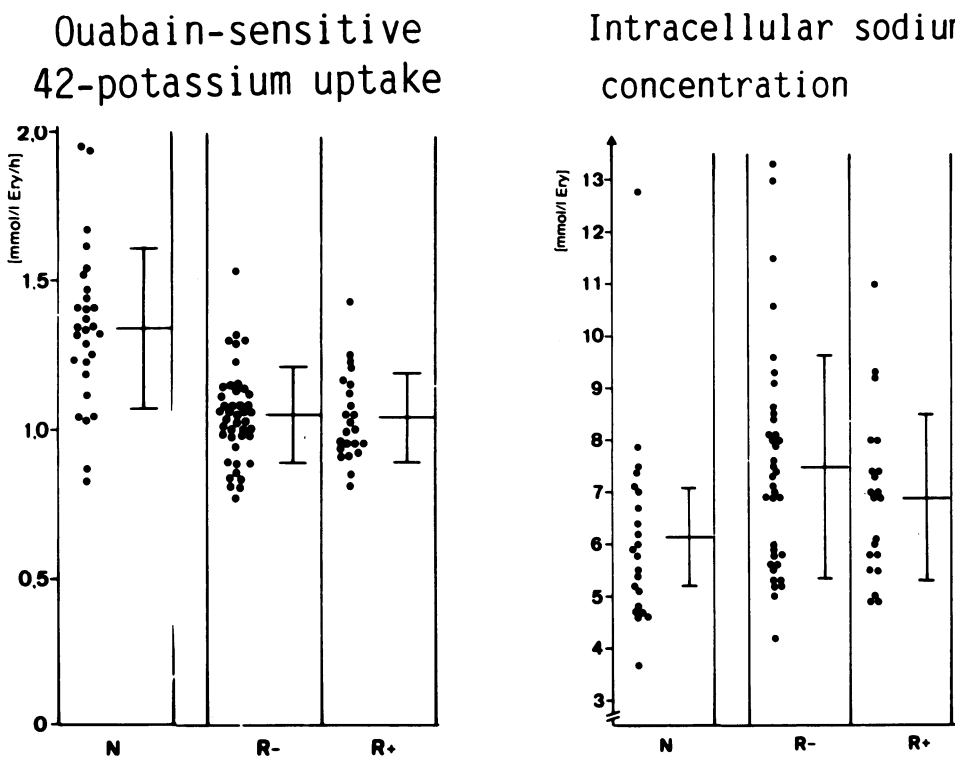

Fig. 7. ^{42}K-uptake by the erythrocytes mmol/l RBC/h and sodium content of the erythrocytes mmol/l RBC in normotensive healthy controls (N) and in renal patients without (R−) and with (R+) hypertension.[27]

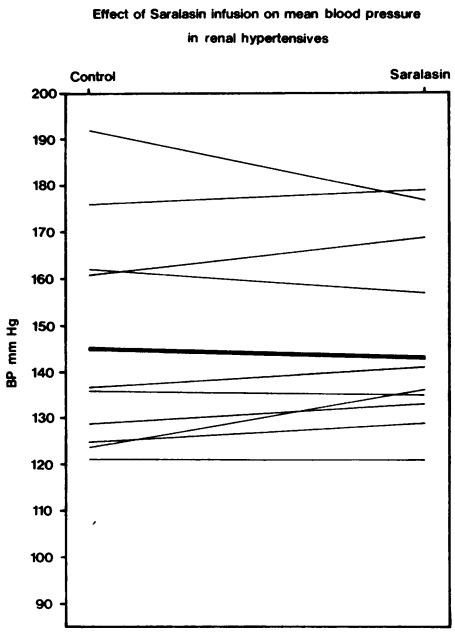

Fig. 8. Effect of a graded one hour-lasting saralasin infusion on mean blood pressure in chronic renal hypertensive patients. Blood pressure fell slightly in only one subject with severe hypertension and elevated plasma renin activity (PRA).[29]

vessels whose ratio wall thickness/vessel lumen is unchanged or raised (Fig 9)[30, 31] and whose compliance is diminished (Fig 5), probably through the inhibition of the Na^+-K^+-pump in the smooth vascular muscles (Fig 7). With the increase of the TPR the cardiac output drops back to its original volume (reflexly?). At this late stage, we cannot rule out the possibility that the renin angiotensin system, whose activity is occasionally raised, may contribute to the development of the high TPR and of the malignant vascular changes,[32, 33] accelerating from now on the downhill course of the disease.

DISCUSSION

The message contained in these studies can be summarised as follows. The haemodynamic alterations leading eventually to hypertension in chronic non-uraemic parenchymatous renal disease do not consist of a generalised vasoconstriction by an overproduction or deficiency of some vasoactive renal agent. Instead, there is a hypervolaemia, due—as shown by the sluggish excretion of the infused saline—to a disturbed renal volume homeostasis, with a subsequent rise in cardiac output and hyperperfusion of tissues. As long as the usual adaptation to this occurs, no change of blood pressure will be observable. Hypertension will develop when this peripheral adaptation is overruled — possibly by the thickening of the previously hyperperfused vessels and by an increased content of the smooth vascular muscles of sodium (and perhaps calcium) due to the inhibition of the Na^+-K^+-pump in the vessel wall by the ouabain-like natriuretic factor released by the initial hypervolaemia of the chronic renal disease.

A few critical words about the methods on which these important conclusions are based must be added. The cardiac output is the mean of at least three successive measurements at 5 to 10 minute intervals under resting conditions, and the difference between the individual data did not exceed 10%. The intra-individual confidence interval between single readings amounted to 8.3%. The error involved in the measurement of the circulating blood volume by the dilution of the ^{113}indium-labelled transferrin on repeated measurements in the same person was $\pm$ 5% and the values agree with those obtained with the ^{51}Cr-labelled erythrocytes. Uncertainty exists about the best reference basis. Whilst our isotope laboratory uses body *weight* for this purpose, it appears that body *height* may be more suitable.[28] We have therefore related our data to both the weight and body surface, the calculation of which includes both these parameters. The results with both these methods revealed the same significant difference between blood volume of the renal hyperkinetic normotensives and all the other subgroups. The slightly higher age (5 years) of group B can hardly be held responsible for a 20%

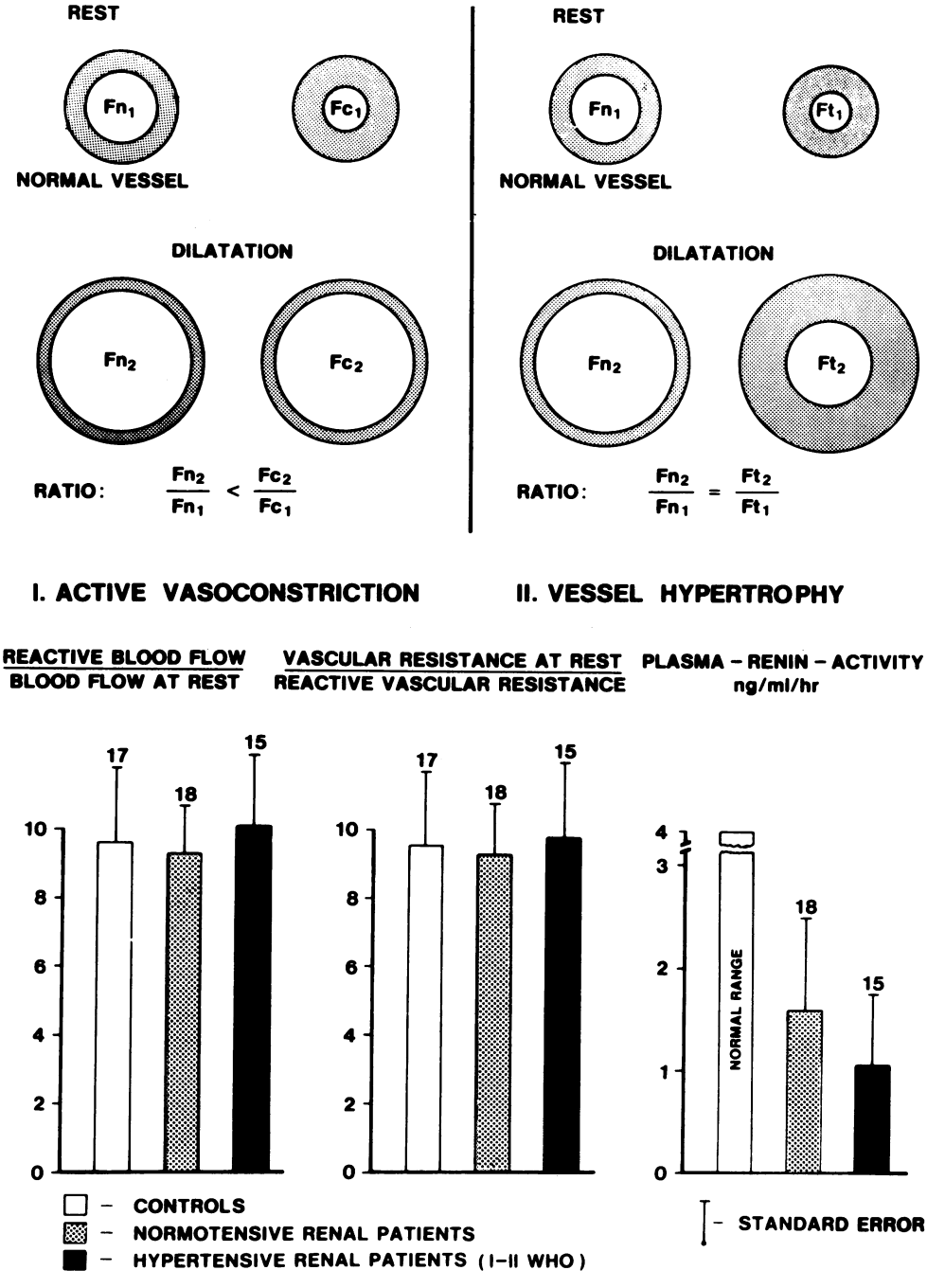

Fig. 9. The ratio 'maximum hyperaemic' to resting forearm blood flow, forearm vascular resistance and plasma renin activity (PRA). A vessel can dilate on the removal of all vasoconstrictor influences only to a given maximum. Hence a constricted vessel will dilate on producing maximum hyperaemia (combination of indirect heating with reactive hyperaemia) more than a previously unconstricted vessel and the ratio maximum flow/resting flow after the removal of vasoconstriction will increase more than with a previously unconstricted vessel.

difference in the cardiac output between groups A and B. We thus could see no other reason why the hypervolaemia and hyperkinesis should be restricted to the normotensive renal patients than that these two changes are the first steps in the development of the haemodynamic abnormality of chronic renal disease leading eventually to hypertension, being analogous to the changes produced by isotonic volume expansion in normotensive subjects with a slight renal defect.

Whereas in healthy normotensive subjects on mild to moderate volume expansion a mechanism analogous to the ANF in rats produces increasing vascular compliance and urine flow, a larger fluid expansion, or a fluid expansion superimposed on a volume of blood *a priori* raised, as in normotensive subjects with a renal defect, will activate the Na^+-K^+-pump inhibiting factor. Whether by this time the vasodilating activity is already exhausted by the protracted hypervolaemia, as suggested by the depletion of the secretory granules in the cardiocytes on volume expansion in rats,[34] or whether in the competition of these two activities (which obviously differ in the mechanism of their action), the ouabain-like factor gains the upper hand, is a matter for further study. Perhaps the sodium- and calcium-loaded vascular smooth muscle cells cannot respond any more to the vasodilating principle.

The ways by which renal disease interferes with the volume homeostatic efficiency of the kidney have still to be explored. Although the GFR of many of the investigated patients was within the normal range, the day and night span of the GFR was reduced in group B, suggesting that the adaptation of this renal function to the exigencies of the volume homeostasis may be restricted. Knowledge of the effect of the various renal parenchymatous diseases on the various intrarenal natriuretic humoral factors, such as the prostaglandins, dopamine[35] or kallikrein, is inadequate. On the other hand it is certain that many other conditions causing hypertension, such as primary aldosteronism (Conn's syndrome), renal artery stenosis or constriction, and intrarenal vasoconstriction, interfere with normal sodium excretion and thus with volume homeostasis.

In essential hypertension there are several possibilities, corresponding perhaps to different etiologies of the disease. There are many indications that the autonomic equilibrium is out of balance, with a 'sympathetic overdrive' starting when the subject was no more than 20 to 30 years of age.[36-40] The consequence is an exaggerated reaction to simple blood pressure-raising stimuli (pain, rage, anxiety) which in the kidney leads to a protracted exaggerated vasoconstriction. The previous reaction may actually merge with the next one and eventually may be present for most of the day, leading to positive water and salt balance. As the sympathetic overactivity may stop during quiet night sleep, the renal vasoconstriction will subside explaining the nocturia of these early essential hypertensives, present in some 60% of cases.[41, 42] There are also age-dependent changes in the kidneys which may be the basis of the blood pressure rise with age,[43] such as the progressive thickening of the glomerular basement membrane with age in rats.[44] Whether this has an analogy in man is so far unknown. The genetic element may have something to do with the renal natriuretic cascade which is still a wide field for investigation.

Thus even a slight restriction of renal function may reduce volume homeostatic efficiency and raise blood pressure. This will re-establish volume homeostasis at a higher blood pressure level. However, the organism has to pay a high price for this compensation by an increased risk of cardiovascular complications which may prove fatal.

APPENDIX

Methods used

Blood pressure	strain gauge, catheter in the femoral artery.
Cardiac output	Indocyanine green dilution, arterial blood drawn from femoral artery.
Total peripheral vascular resistance (TPR)	$\frac{\text{mean BP (electronically integrated)}}{\text{cardiac output/60}} \times 1332\ \text{dyn.cm}^{-5}\ \text{sec.}$
Forearm blood flow	Whitney occlusion plethysmograph.
Forearm vascular resist.	$\frac{\text{mean blood pressure}}{\text{forearm blood flow/60}} \times 1332 \times 10^{-5}$
Forearm blood volume	^{113}indium-transferrin dilution in the forearm ½ hour after its injection by a central catheter is quantitatively calibrated by the increase in both volume ($\triangle V$) (measured plethysmographically) and radioactivity ($\triangle A$): $\frac{\triangle A}{\triangle V} = \frac{A}{V}$
Venous distensibility (compliance)	Forearm blood volume/forearm venous pressure
Central venous pressure	Catheter in superior vena cava close to the atrium.
Plasma renin activity (PRA)	Isotope double dilution technique.
Glomerular filtration rate (GFR)	Mean of the endogenous creatinine clearance for two 12-hour periods.

This paper is dedicated to the memory of my friend Mr Max Freeland, to whose great organisational skill, untiring endeavour and advice this Unit owes much of its present existence.

I would like to express my sincere thanks to my colleagues Prof J Bahlmann, Prof M Cachovan and Dr P Pretschner who shared with me the excitement of the laboratory work during the past 10 years and to Miss Maria Futterová who was an excellent technical assistant.

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Hyperparathyroid bone disease in chronic renal failure

T Cundy, N Hamdy, R Gray, B Jackson, J A Kanis

SUMMARY

Much has been learnt over the past 80 years of the pathogenesis and management of hyperparathyroid bone disease in uraemia. Clinically it has changed from a rare disorder of childhood and adolescence to a common and difficult problem in patients maintained on dialysis programmes. Whereas effective treatments are now available for hyperparathyroid bone disease, these are not curative and there is clearly much more work to be done before a full understanding of its pathogenesis, and the best methods of treatment and prevention, can be reached.

INTRODUCTION

The skeletal abnormalities found in chronic renal failure are collectively termed renal osteodystrophy or renal bone disease. These include parathyroid bone disease, osteomalacia, osteoporosis, osteonecrosis, osteosclerosis and periosteal new bone formation. The pathogenesis of these disorders has been greatly clarified since the inception of regular dialysis programmes for treatment, with the result that treatment strategies have become defined more accurately and in some instances have proved more successful.[1-4] This article considers the bone disease related to increased secretion of parathyroid hormone which gives rise to parathyroid bone disease or osteitis fibrosa.

Abnormalities in parathyroid function have been known to occur in renal failure since the turn of the century,[5] but, in the earlier reported cases, significant clinical problems were rare, except in children.[6, 7] It was only with the development of supportive treatments for renal failure, such as dialysis and transplantation, that patients survived long enough to develop symptomatic bone disease. This in turn provided a major stimulus to understand the disorder, even though hyperparathyroid bone disease is not exclusive to renal failure.

THE NATURE OF HYPERPARATHYROID BONE DISEASE

Bone is a self-repairing tissue and normally undergoes a sequence of cellular events to ensure that skeletal mass and architecture are maintained.[8] In the adult skeleton, this process is termed 'remodelling' and comprises three phases which occur on the trabecular surfaces of bone. The first is the resorption of a packet of mineralised bone by the action of bone resorbing cells, the osteoclasts, and takes one or two weeks to be completed. Following the completion of a resorption cavity, osteoclasts leave the bone surface and are replaced by osteoblasts which lay down unmineralised bone matrix (osteoid) in an orderly lamellar array at the site of previous bone resorption. Some osteoblasts become trapped within the

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osteoid matrix to form osteocytes, and it is thought that these are responsible for the third phase of bone remodelling which is the mineralisation of this organic collagen matrix. The remodelling sequence is therefore a phenomenon occurring at bone surfaces and does not take place at the same rate in all parts of the skeleton. For example, bone turnover is more rapid in trabecular bone than in cortical bone where the surface-to-volume ratio is low.

Parathyroid hormone is an important activator of this remodelling sequence. In the presence of high secretion rates of parathyroid hormone, the frequency of activation of these remodelling packets is increased.[8] The histological consequences are that an increased proportion of the bony surface is involved in both resorption and formation and less of the bone surface is resting. The rapid rates of bone resorption are associated with irregular excavations on the bone surface which can be detected histologically. Local imbalances in formation and resorption may result in patchy osteopenia, particularly of cortical bone. A further consequence of rapid rates of bone remodelling is that new bone formed is laid down in a haphazard fashion rather than in an orderly lamellar array (woven osteoid). This calcifies gradually to form woven bone occupying a relatively large volume, and the total bone volume may increase in hyperparathyroid bone disease so that osteosclerosis and osteoporosis co-exist in the same patient. These consequences of increased bone turnover impair both the structure and the mechanical properties of bone. An additional consequence of increased bone resorption is the deposition of fibrous tissue within the marrow cavity giving rise to the term 'osteitis fibrosa' for hyperparathyroid bone disease (Fig 1).

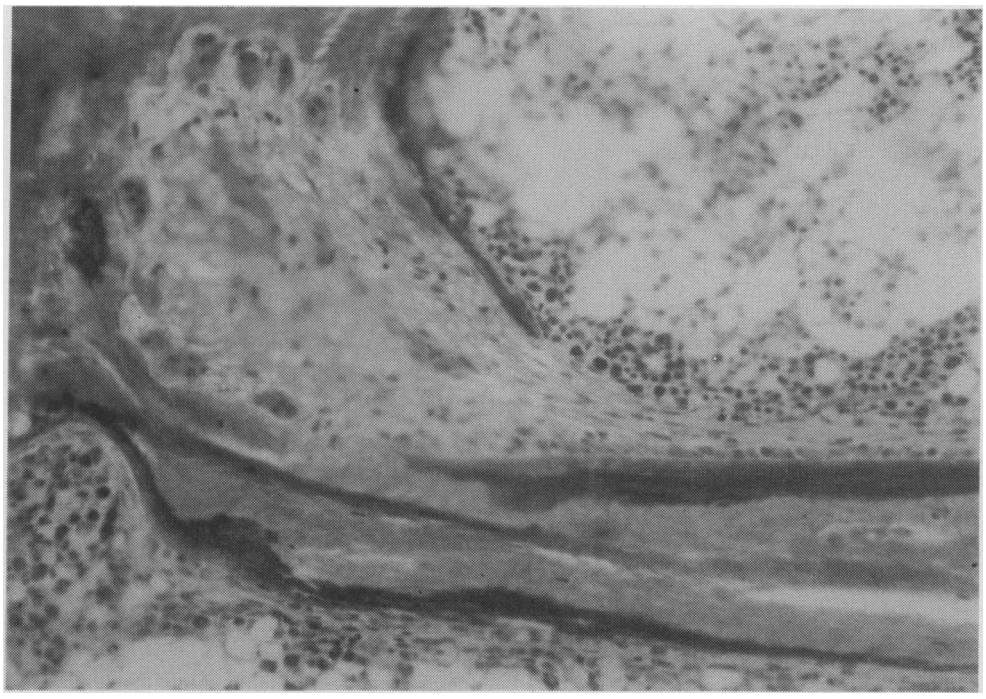
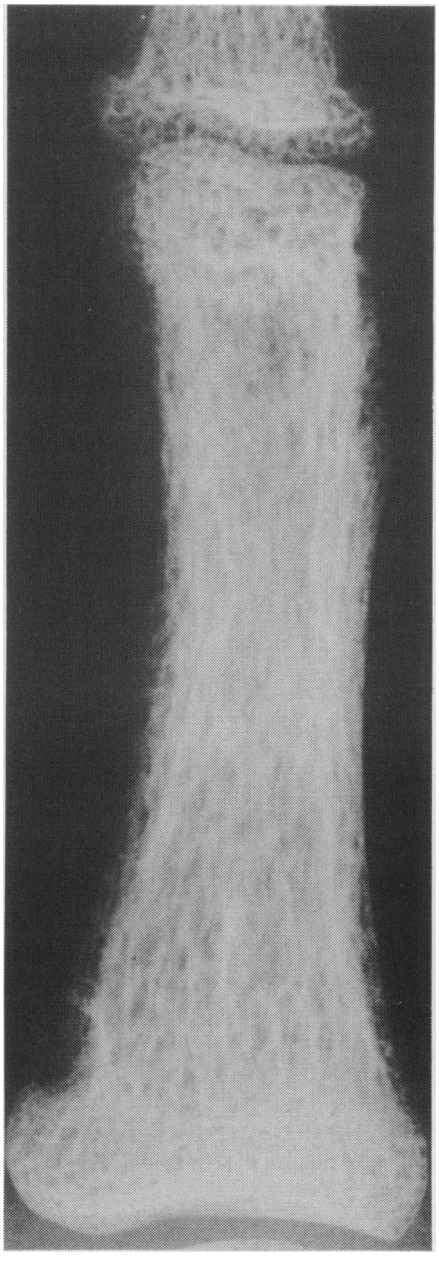


Fig. 1. Histological features of parathyroid bone disease in renal failure. Most of the unmineralised bone surface is occupied by multinucleated osteoclasts resorbing bone. The osteoid surface is increased due to an increase in the number of bone-forming cells. Marrow fibrosis occupies chiefly the resorption cavity but also extends over the formation surface.

Fig. 2.

Radiographic features of parathyroid bone disease in renal failure. Alternate bands of osteosclerosis give rise to the 'rugger jersey' appearance.



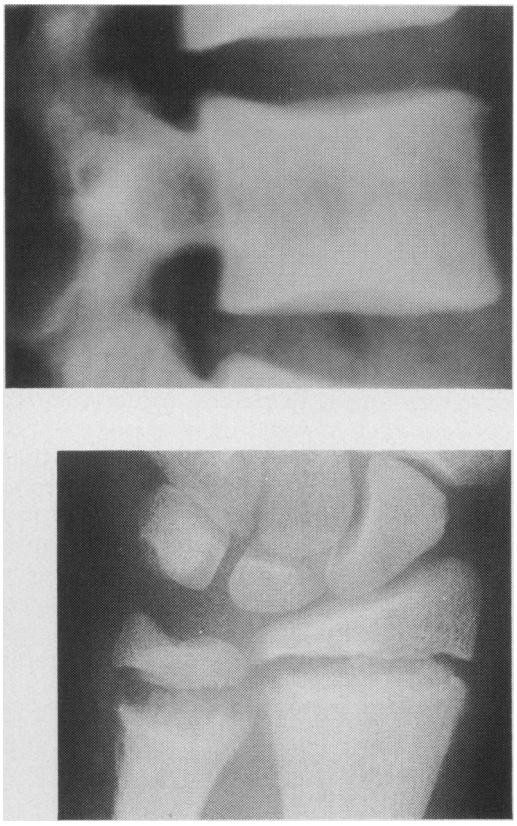


Fig. 4.

X-rays of the wrist to show marked metaphyseal erosion due to hyperparathyroidism in an adolescent (above).

The X-ray below shows the response to treatment with 1α-OHD_3.

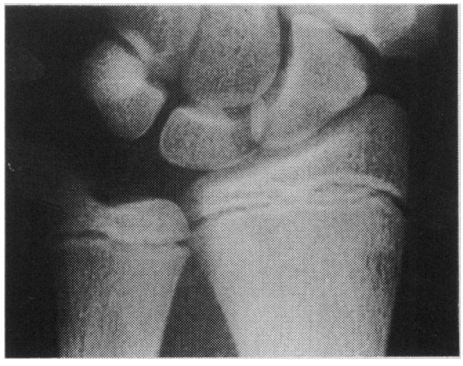


Fig. 3.

Marked sub-periosteal erosions of bone in hyperparathydroism. Erosions are more marked on the radial aspect of the phalanx (left).

FEATURES OF HYPERPARATHYROID BONE DISEASE

Osteosclerosis is frequently noted in skeletal radiographs, particularly in the spine (Fig 2), but the characteristic radiographic feature of hyperparathyroid bone disease is subperiosteal erosion of bone. Erosions are found most frequently in the radial borders of the phalanges, the distal ends of the clavicles and the terminal phalanges (Fig 3). Gross erosion of the terminal phalanges (acro-osteolysis) may result in the collapse of soft tissue, normally supported by bone, giving rise to the appearance of pseudo-clubbing. In children, erosions are commonly found in the metaphyseal region of long bones where the rate of bone remodelling is high (Fig 4). Periosteal new bone formation is a less common feature in renal hyperparathyroidism (Fig 5).

Plasma or serum alkaline phosphatase activity is a useful biochemical marker of bone remodelling, since the bone-derived fraction reflects the numbers of active osteoblasts. Plasma hydroxyproline, reflecting in part bone collagen destruction by osteoclasts, may also be used as a biochemical marker, but in renal hyperparathyroidism resorption and formation are both increased to a similar extent, and there is little advantage in measuring both, except for the investigation of treatment régimes.[9]

Clinically, hyperparathyroid bone disease may give rise to bone pain, tenderness and to muscle weakness. Children and adolescents are affected more frequently and more severely than adults. Metaphyseal erosions in the growing skeleton seen on x-rays may bear some resemblance to rickets (Fig 6), but may give rise to marked skeletal deformities (Fig 7). It is for these reasons that almost all the early descriptions of renal bone disease related to children and adolescents.[6, 7]

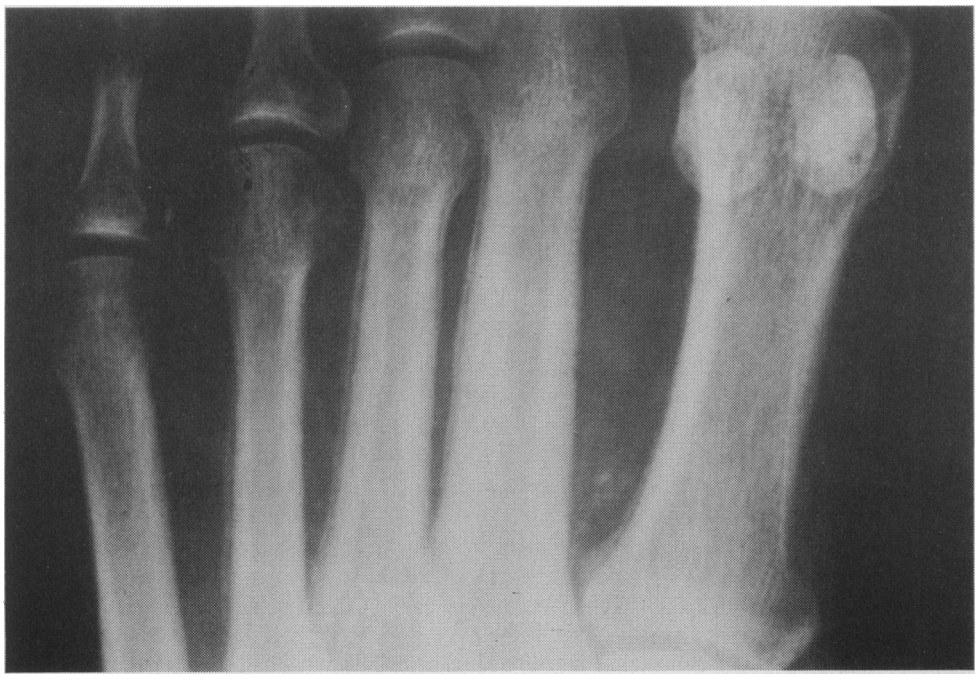


Fig. 5. Sub-periosteal new bone formation in hyperparathyroid bone disease. Note the periosteal elevation along the shafts of the metatarsals.

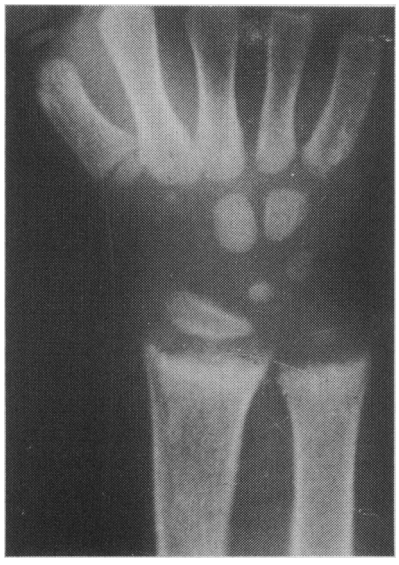


Fig. 6. Radiographic features of rickets. Note the widened epiphyseal plate and splayed metaphysis which contrasts with the metaphyseal erosion of hyperparathyroidism (Fig 4).

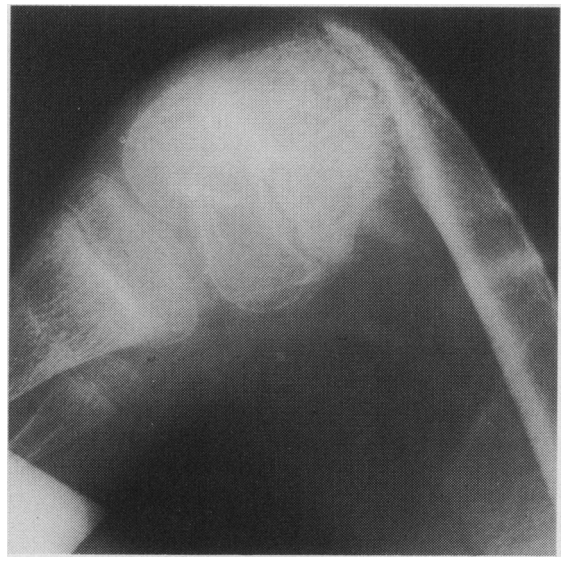


Fig. 7. Severe metaphyseal bone resorption in the femur of an adolescent uraemic.

Symptomatic bone disease occurring before end-stage chronic renal failure is relatively uncommon in adults[10] and suggests the presence of additional disorders interfering with skeletal metabolism, such as nutritional deficiency of vitamin D.

The prevalence of hyperparathyroid bone disease in patients reaching end-stage chronic renal failure depends on the criteria used for diagnosis. The bones of most patients show some changes of hyperparathyroidism when examined microscopically as judged by increased numbers of bone-forming and bone-resorbing cells, but only 30-40% have significant degrees of osteitis fibrosa. Less have radiographic changes and a small minority have symptoms. In patients maintained on haemodialysis treatment the incidence rises, but symptoms are still confined to a minority in most dialysis centres (10-15%).[10]

PATHOGENESIS OF HYPERPARATHYROID BONE DISEASE

There is little doubt that hyperparathyroid bone disease is due to an increased secretion of parathyroid hormone (PTH) by the parathyroid gland. Eighty years have now passed since the first description of parathyroid gland enlargement in uraemia,[5] and it has been known for 50 years that this was a common finding.[12] However, it is only recently that the causes of increased parathyroid secretion in uraemia have become clarified.

Abnormalities in phosphate transport appear to be of great importance. The kidney is a major route for the excretion of phosphate, and when renal function fails the serum phosphate rises. Albright in the 1930s was the first to speculate on the importance of phosphate retention in causing hyperparathyroidism in renal failure by suggesting that hyperphosphataemia might lower serum calcium values, which would in turn stimulate the parathyroid gland.[13] This theory was later refined by elegant experimental evidence from Slatopolsky and Bricker and

their colleagues,[14] who were able to delay the development of hyperparathyroidism in dogs with progressive renal failure by decremental reductions in dietary phosphate. In contrast, dogs who were allowed unrestricted dietary phosphate developed hyperphosphataemia and hyperparathroidism as their renal function declined.

The discovery that the kidney was the major site of conversion of vitamin D to its biologically active form, 1,25-dihydroxyvitamin D_3 (calcitriol),[15] provided another important clue in understanding the pathogenesis of hyperparathyroid bone disease. Progressive loss of renal tissue and the associated hyperphosphataemia impair the enzyme responsible for the production of this hormonal form of vitamin D, in turn responsible for calcium absorption from the gut. Diminished intestinal absorption of calcium may therefore aggravate hypocalcaemia and, in turn, increase the secretion of parathyroid hormone and the size of the parathyroid gland.

These hypotheses (Fig 8) have been partially tested in man, but there are still some gaps in our knowledge. Although these mechanisms are an oversimplification, they nevertheless provide a useful background on which to investigate affected patients and to design and test various treatment strategies. Not all uraemic patients have bone disease, nor will all develop bone disease, despite the ubiquity of phosphate retention and impaired synthesis of calcitriol. It becomes relevant, therefore, to pose the question as to why some patients do not develop bone disease and others are at particular risk. Several factors appear to predispose to renal bone disease at the time of starting dialysis treatment. Not surprisingly, these include young age and a long duration of renal disease. Tubulo-interstitial forms of renal disease more commonly give rise to renal bone disease than glomerular forms: probably this is related to the destruction of the tubular cells responsible for the metabolism of vitamin D. Women have recently been identified as being at particular risk from renal bone disease, and impaired ovarian steroid production may therefore be an important determinant of the susceptibility to hyperparathroidism.[10]

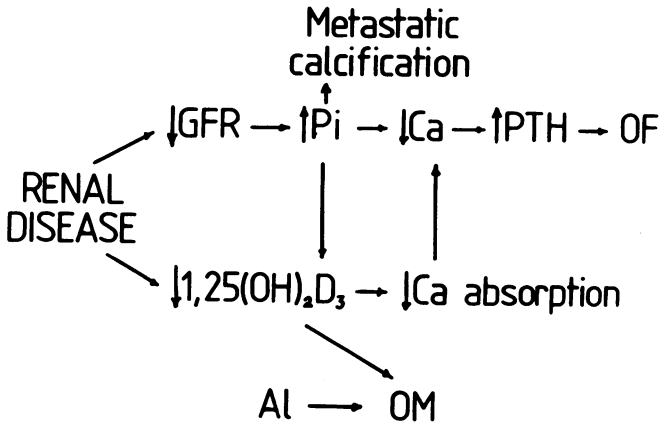


Fig. 8. The role of vitamin D and parathyroid hormone in the pathogenesis of renal bone disease. Progressive renal disease induces decrements in glomerular filtration rate (GFR) and synthetic capacity for calcitriol ($1,25(OH)_2D_3$) giving rise to osteomalacia (OM). An increase in plasma phosphate (Pi) due to the fall in GFR stimulates the secretion of parathyroid hormone (PTH) indirectly by decreasing plasma calcium levels (Ca). Malabsorption of calcium may contribute to secondary hyperparathroidism. During progressive renal failure plasma calcium and phosphate tend to remain normal (because of the renal and skeletal effects of PTH) at the expense of an increasing secretion rate of PTH and its skeletal consequence, osteitis fibrosa (OF). When the compensatory abilities of the kidney are compromised by renal failure, hyperphosphataemia and hypocalcaemia prevail. Retention of aluminium may also cause osteomalacia.

THERAPEUTIC APPROACHES

Haemodialysis and chronic peritoneal dialysis provide the opportunity for manipulating the biochemical environment, which can modify bone disease. In many instances hyperparathyroid bone disease may regress, but sometimes at the expense of other forms of bone disease. With respect to skeletal metabolism, the institution of dialysis results in an increase in serum calcium and a decrease in serum phosphate towards normal values. Adequate control of serum phosphate may not be achievable by dialysis alone and often requires the use of antacids such as aluminium hydroxide which bind phosphate in the gut and render it unavailable for absorption. Despite these dramatic biochemical improvements, hyperparathyroid bone disease increases both in severity and frequency with increased duration of dialysis (Fig 9) in most renal units (except those in which aluminium toxicity is endemic). The normalisation of serum calcium might be expected to suppress PTH secretion, and in the short term it appears to do so. Thus, after patients have begun regular haemodialysis, plasma values of alkaline phosphatase decrease towards normal, and sub-periosteal erosions may heal. These improvements are, however, transient, and bone disease tends to recur despite the maintenance of normocalcaemia. A similar approach has been to increase serum calcium values above normal by the use of high concentrations of calcium in the dialysis fluid.[16] Once again, any improvements which occur in hyperparathyroid bone disease are transient and are offset by the increased risk of extraskeletal calcification. In a recent study of long-term survivors on maintenance haemodialysis, two-thirds of patients dialysed for 10 or more years required parathyroidectomy.[17]

The two mainstays of treatment of parathyroid bone disease have been the use of vitamin D derivatives and parathyroidectomy. The choice of treatment has changed somewhat over the years. Problems with the unpredictable content and formulation of vitamin D, vitamin D toxicity and dangers of increasing extra-skeletal calcification made the use of high doses of vitamin D unpopular. As a result, in the early 1970s, the more radical approach of parathyroidectomy was favoured.[18] The discovery of the renal 1α-hydroxylase system[15] and the subsequent availability of calcitriol and its synthetic analogues, 1α-hydroxyvitamin D and dihydrotachysterol has refocussed attention on the use of preparations of vitamin D.[2, 3]

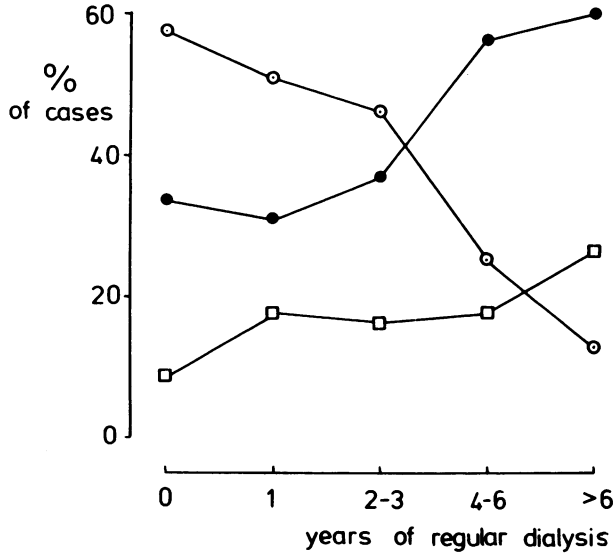


Fig. 9. Natural history of renal bone disease in 207 patients receiving dialysis treatment at the Oxford Renal Unit. The prevalence of osteitis fibrosa (with or without osteomalacia) (●) and osteomalacia alone (□) both increased with time, though changes in the former are more marked. In the 78 patients dialysed for 6 years or more, only 13% had no evidence of marked disease (o).

Vitamin D may act simply by increasing intestinal absorption of calcium and thereby raising the serum calcium, but some recent research has suggested that it may also act directly on parathyroid tissue to suppress its secretion. The evidence that this contributes to a therapeutic response is not clear. Even less clear is the question whether or not vitamin D may have a direct action on the skeleton. Thus, the use of metabolites of vitamin D may improve hyperparathyroid bone disease by mechanisms in addition to raising serum calcium, but this requires more investigation.

The short-term responses of many manifestations of hyperparathyroid bone disease are now well documented in response to treatment with vitamin D derivatives. Bone pain improves, subperiosteal and metaphyseal erosions heal, serum alkaline phosphatase and hydroxyproline values fall, and growth in children may accelerate.[19-22] In dialysis-treated patients, the long-term results are not so reassuring. The histological changes in bone are not as striking as the clinical, biochemical and radiographic improvements,[23] and dialysis-treated patients appear to respond less favourably than less uraemic patients.[24, 25] Moreover, following long-term treatment, hyperparathyroidism tends to recur despite continued treatment and the maintenance of normal or high plasma calcium levels (Fig 10).[26] Although the newer vitamin D compounds are much easier to control,[27] the outcome of therapy with them is comparable to those observed with high doses of 25-hydroxyvitamin D or vitamin D_2.[28, 29] Nevertheless, the improvement in hyperparathyroid bone disease may persist for many years and thus vitamin D remains a valuable adjunct to management.

Parathyroidectomy remains an important component of the management of patients with hyperparathyroid bone disease. Though still a matter for debate,

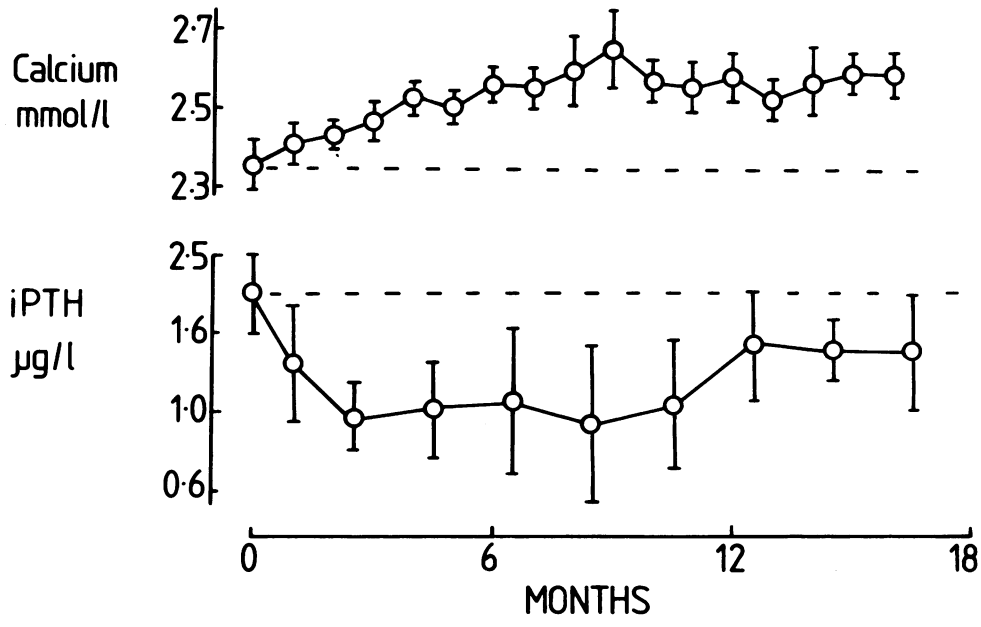


Fig. 10. Sequential changes in plasma calcium (mean±SEM), and serum immunoassayable parathyroid hormone (iPTH) in 13 patients treated continuously with 1α-OHD_3. Note the sustained increase in plasma calcium but ill-sustained suppression of iPTH.

partial parathyroidectomy may be preferable to removal of all parathyroid tissue. However, the long-term follow-up of patients following partial parathyroidectomy indicates that this treatment, like many others for hyperparathyroid bone disease, has transient effects, and bone disease tends to recur despite the concurrent use of vitamin D and the maintenance of normocalcaemia.[30] The remission period is probably longer than that observed in patients treated with vitamin D preparations alone. One of the reasons for avoiding total parathyroidectomy is that this may precipitate a refractory form of vitamin D-resistant osteomalacia,[31] similar to that observed in patients with aluminium retention.

A partial or transient suppression of hyperparathyroidism in dialysis-treated patients therefore seems possible to achieve in a number of ways. These include phosphate restriction, the infusion of calcium via the dialysate, the use of vitamin D derivatives or parathyroidectomy. Despite the efficacy of these methods, bone disease tends to recur, and it is clear that in dialysis patients there remains a potent stimulus to the growth of parathyroid tissue in addition to low values of serum calcium. The vigour with which parathyroid tissue continues to grow has been demonstrated in studies of auto-transplanted parathyroid tissue removed from patients with hyperplastic glands and embedded in sternomastoid or forearm muscles. Such transplanted tissue may become disseminated and histologically demonstrate paramalignant behaviour by locally invading blood vessels and muscle tissue.[32, 33] The nature of this stimulus to parathyroid growth is not known. Research of this aspect of parathyroid function is in its infancy and provides one of the challenges for the future.

We are grateful to the National Kidney Research Fund and the Trent Regional Health Authority for their support of our work.

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Current problems in continuous ambulatory peritoneal dialysis

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SUMMARY

In spite of multiple problems, continuous ambulatory peritoneal dialysis is now an acceptable alternative treatment for end-stage renal failure. With proper care and attention to detail, many of its problems can be reduced or eliminated. It is particularly suitable for the very old, the very young and the patient living a long distance from the centre, and it is the treatment of choice for diabetes mellitus prior to transplantation.

INTRODUCTION

Continuous ambulatory peritoneal dialysis was commenced in the Meath Hospital, Dublin, in January 1980. The experience and complications noted from many other centres with the development of CAPD prompted us to establish our own protocol. From the onset, a nurse (G.G.) with responsibility solely for the training and follow-up of CAPD patients was appointed in the renal unit. It was planned to employ further nursing personnel as numbers increased.

PATIENTS AND METHODS

During the period January 1980 to July 1984, 68 patients were treated with CAPD and 37 patients are currently being treated. Patients chosen for CAPD initially were high-risk patients not suitable for haemodialysis; but subsequently all patients were given the option to choose CAPD provided the nephrologist and the CAPD nurse considered them suitable candidates.

Initiation of CAPD involved the insertion of a chronic Tenckhoff catheter into the peritoneal cavity and this was undertaken by the consultant urologist. Following insertion of the catheter under general anaesthetic in the operating theatre using the open technique, the patient returned to a general medical ward and the catheter was flushed with small volumes of fluid to ensure patency. The volume was gradually increased to the required amount. CAPD was commenced when the blood urea and serum creatinine levels reached acceptable levels. Most of the patients were maintained perfectly well on three bag exchanges per day, using Travenol System 1 solutions (Spike System), but those who had negligible or no endogenous renal function or whose body weight was too large required four exchanges daily. The training period of the patients took ten to fourteen days. Patients were reviewed at the renal clinic on a monthly basis. The connector tubing was changed every six weeks to two months. Patients received a mean protein intake of 80-100 g per day with moderate restriction in salt and phosphorus. Fluid intake was not restricted unless ultrafiltration problems arose.

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Most of the patients treated peritonitis at home and every patient's training included instruction in the early recognition of peritonitis and its treatment. The importance of sending samples of peritoneal effluent, properly taken as soon as the symptoms occurred, was stressed. All debilitated patients and patients with severe peritonitis were admitted to hospital.

RESULTS

Peritonitis was the most serious problem associated with CAPD, because, if septicaemia resulted, life could be threatened, ultrafiltration decreased and the efficacy of dialysis reduced. Peritonitis was diagnosed when a patient had two of the following symptoms: cloudy effluent, abdominal pain or fever, and a positive bacterial culture.

The differential diagnosis included infective peritonitis (when the patient had cloudy effluent with or without abdominal pain and a positive bacterial culture); aseptic peritonitis (when the patient had cloudy effluent and abdominal pain but negative bacterial cultures); eosinophilic peritonitis (when the patient had cloudy effluent showing eosinophils, but no pain or negative bacterial cultures). Other causes of cloudy effluent included constipation, diarrhoea, menstruation, cholecystitis, pseudomembranous colitis and coeliac disease. Causative organisms found in the Meath Hospital were mainly gram-positive cocci — staphylococcus albus, staphylococcus aureus and streptococcus species. Gram-negative organisms which were usually hospital-acquired included acinetobacter, pseudomonas species, serratia species, enterobacter species, and escherichia coli. Fungi were mainly candida.

Treatment of peritonitis was based on three fast exchanges with heparin added, a loading dose of antibiotics intraperitoneally, and a maintenance dose six-hourly intraperitoneally for seven days. Heparin was added to each bag for the seven days. First-line therapy was cefuroxime and cloxacillin; and second-line therapy was netilmicin. Resistant staphylococcus albus was treated with vancomycin intraperitoneally, and vancomycin was administered intraperitoneally as a first line treatment for patients known to have relapsing staphylococcus albus infections. Fungal infections were treated by hourly to four-hourly exchanges using small volumes of dialysate containing miconazole and heparin, until a positive fungal culture was obtained. The Tenckhoff catheter was then removed as early as possible and replaced immediately with an acute catheter. Rapid lavage was commenced immediately using small volumes of dialysate containing miconazole and heparin. Ketoconazole was also administered orally. The Tenckhoff catheter was replaced when fluid was microbiologically clear on three consecutive days. Persistent infections were treated by removing the Tenckhoff catheter.

Infection rates were as follows:

1980 — 1/6.3 patient months.
1981 — 1/8.1 patient months.
1982 — 1/5.1 patient months.
1983 — 1/9.0 patient months.
1984 to June — 1/10.1 patient months.

The high infection rate in 1982 may be accounted for by the change-over from System 1 (spike system) to System 2 (Luer lock system), and the change-over to single-line antibiotic therapy. The initial 'high-risk' patient complement was

experiencing various serious problems. Prevention of peritonitis lies in the better selection and training of patients, revision of training at intervals, further improvements in equipment such as the Ultra Violet System (UV System) and more durable infusion sets; and a team who are interested in the treatment.

Catheter problems can be divided into early or late problems. Early dialysate leak was usually prevented by good catheter positioning and conditioning, but, if early leak occurred, it responded to a reduction in the fluid amount or suspension of the dialysis for 24 to 48 hours. Early two-way obstruction responded to flushing with heparin. Early one-way obstruction caused by omental wrapping usually resulted in catheter removal.

Late catheter problems included exit site infection. Omission of a suture around the catheter and frequent dressings during the first week helped to prevent this. Daily showers and washing of the exit site with povidone iodine were advised and the catheter was held in position with elastoplast. Weekly dressing with opsite which held the catheter firmly in position was carried out on patients who preferred to have a dressing. If infection did occur, the exit site was dressed daily with antibiotic cream, and if the infection did not improve an appropriate oral antibiotic was commenced and continued for seven to 14 days. Tunnel infection may or may not be associated with exit site infection but, if it is, it may be curtailed by removing the subcutaneous cuff and the infected area from around the catheter, under strict sterile conditions in the operating theatre. Tunnel infection usually led to persistent peritonitis which necessitated removal of the catheter. Extrusion of the subcutaneous cuff was treated by shaving off the cuff in the operating theatre under strict sterile conditions. Late two-way obstruction responded to flushing with heparin. Late one-way obstruction was caused by kinking of the catheter or migration of the catheter from its original position. Repositioning of the catheter was attempted but catheter replacement was usually necessary. Late dialysate leak occurring around the catheter responded to a reduction in the fluid amount or suspension of dialysis for 24-48 hours. More serious were leaks into the pleural cavity, the vagina and the scrotum.

Lack of ultrafiltration may have been caused by a decrease in residual renal function as time on dialysis increased, but it was usually caused by severe prolonged peritonitis and its treatment, leading to hypoalbuminaemia, rapid glucose absorption and fluid overload. Treatment consisted of 3.86% dextrose solutions with long dwell times with an occasional two-hourly exchange of 3.86% dextrose to allow for better ultrafiltration. High protein diet was encouraged, fluid and salt were restricted and in some cases high doses of frusemide were used.

Three patients developed an acute confusional state while on fast exchanges which reversed on return to normal dialysis regimen. Two of these patients had evidence of widespread atherosclerosis. Some patients developed postural hypotension caused by dehydration and antihypertensive treatment. Treatment consisted of the introduction of salt and increased fluids. Hypotensive agents and fast exchanges were discontinued.

Three patients developed radiological evidence of renal osteodystrophy:

C.B. age 69 years — CAPD for four years.

B.R. age 70 years — CAPD for three years.

A.M.H. age 45 years — CAPD for one year; had previously been on haemodialysis.

Hernias which were caused by extra fluid load in the abdomen were repaired surgically without interruption of CAPD. Intestinal obstruction in one patient was caused by adhesions around the dacron cuff.

Two patients developed right-sided pleural effusions. They were significant in that both were right-sided and a radio opaque dye injected into the peritoneal cavity appeared in the pleural fluid. In addition, the biochemical composition of the pleural fluid was similar to the drained dialysate. Both were treated by pleurodesis, one remaining on CAPD without interruption and the other returning to haemodialysis for one week. Two patients developed hyperlipidaemia.

Hypoalbuminaemia was caused by fast exchanges and malnutrition, and by peritonitis and its treatment. Treatment consisted of curtailing fast exchanges and encouraging high protein diet. Minor problems included low back pain, shoulder pain, constipation, cramps, bleeding, gastric problems such as reflux oesophagitis and hiatus hernias, sexual problems which were usually associated with the catheter, and equipment problems.

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The efficacy and adequacy of continuous ambulatory peritoneal dialysis

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SUMMARY

Since it was introduced in 1976, continuous ambulatory peritoneal dialysis (CAPD) has won acceptance in many centres and it is now regarded as an important alternative to haemodialysis. CAPD patients have comparable and, in some circumstances, better survival than those on chronic haemodialysis. It is indicated particularly in patients with diabetes mellitus, cardiovascular instability and at the extremes of life. The success of kidney transplantation is similar in those maintained on CAPD and on haemodialysis. CAPD also achieves satisfactory physical and psychological rehabilitation, and the quality of life, including the level of sexual function, is similar during CAPD and haemodialysis. Women on CAPD menstruate more often than those on haemodialysis. CAPD provides adequate clearance of metabolic wastes, maintains fluid balance and ameliorates neurotoxic cognitive dysfunction. CAPD gives control of hypertension and anaemia which is superior to that on haemodialysis. Neuropathy remains stable but osteitis fibrosa seems to progress. CAPD is the most economical of the various forms of dialysis. We conclude that CAPD is an adequate form of replacement and should be made available in every nephrology centre providing treatment for patients with end-stage renal disease.

INTRODUCTION

Continuous ambulatory peritoneal dialysis (CAPD) was introduced in 1976[1] and soon became one of the most popular modes of home dialysis. There is no single qualitative or quantitative index by which to evaluate the efficacy of CAPD. This paper will present evidence to suggest that CAPD provides adequate dialysis according to the following criteria:

1) It sustains life in patients with end-stage renal disease (ESRD).
2) It maintains patients in a satisfactory condition while awaiting a kidney transplant, and it does not adversely affect the results of transplantation; if the latter fails, CAPD can be recommenced after transplant nephrectomy.
3) It provides a satisfactory quality of life as indicated by adequate rehabilitation and sexual activity.
4) It can sustain children, and facilitate their growth.
5) It can provide adequate biochemical control.
6) It can arrest or even ameliorate uraemic complications.

Furthermore, it is an inexpensive process.

In addition the adequacy of CAPD will be demonstrated by comparing its results with those of the more firmly established dialysis modality — chronic haemodialysis.

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SURVIVAL ON CAPD

In Toronto Western Hospital, survival at the end of 1, 2, 3, 4, 5 years is 90%, 80%, 70%, 65% and 46% respectively (Fig 1). The attrition rate is about 10% per year.

Data concerning the various forms of dialysis used in Canada in 1981-1982[2] shows that the non-diabetic CAPD patients (n = 596), who were, on average, 4 years older than those on haemodialysis, have a 90% and 80% chance of survival at the end of 12 and 24 months respectively. During this same period, the non-diabetics on haemodialysis (n = 1161) had a survival rate of 85% and 75%. At the end of two years, the probability of dropout (failures and deaths together) was 48% on CAPD, and 41% on haemodialysis. Thus by these criteria the two modalities were comparable.

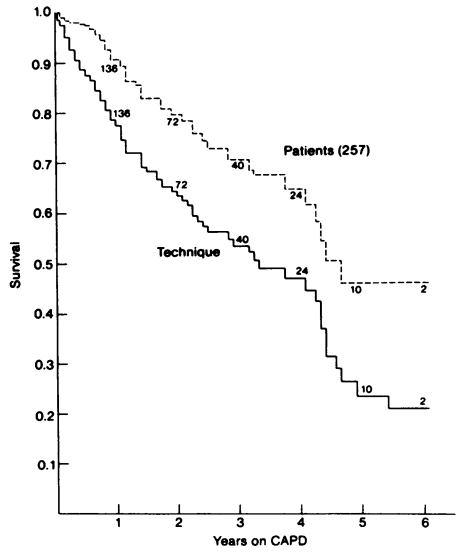

Fig. 1. Cumulative patient and technique survival in 257 CAPD patients at the Toronto Western Hospital.

The European Dialysis and Transplant Association (EDTA) studied a large number of CAPD patients and compared them with patients on other replacement therapies.[3] They had 3607 patients registered on CAPD by the end of December 1982. Their data showed that the survival of CAPD patients in various age groups is comparable with that on other modalities (Tables Ia and Ib). In all age groups, survival of diabetics on CAPD at one year was consistently better than that of the general diabetic population on renal replacement therapy, although no statistical analysis was provided.

TABLE Ia

One-year survival among non-diabetic patients with end-stage renal disease being treated with kidney replacement therapy in Europe

	Therapy (% of patients alive)			
Age (year)	*Haemodialysis*(1)	*CAPD*	*Cadaveric transplant*	*Any kidney replacement therapy*(2)
15 – 34		97	93	93
35 – 44		96	90	91
45 – 54	90	92	84	90
55 – 64		84	77	85
65		75	77	76

(1) Value extracted from a figure.

(2) Irrespective of any subsequent changes in the mode of treatment.

TABLE Ib

One-year survival among diabetic patients with end-stage renal disease being treated with kidney replacement therapy in Europe

	Therapy (% of patients alive)			
Any (year)	Haemodialysis[1]	CAPD	Cadaveric transplant	Any kidney replacement therapy[2]
15 – 34		92	72	77
35 – 44		77	77	73
45 – 54	72	80	63	71
55 – 64		71		70
65				58

(1) Number extracted from a figure.
(2) Irrespective of any subsequent changes in the mode of treatment.

Of the factors which influence survival, the most important are age, diabetes, pre-existing cardiovascular disease and depression at the onset of treatment. Survival at four years for patients younger than 40 years, those between 40 and 59, and those older than 60 were 95%, 72% and 40% respectively. This is not surprising because, in general, younger patients are healthier and have fewer cardiovascular and metabolic complications.

Patients with end-stage renal failure due to diabetes are particularly difficult to treat. They have multiple system involvement and significant impairment of visual acuity. Their survival on intermittent peritoneal dialysis is poor.[4] Many diabetics with end-stage renal failure, even those who are blind, are now treated with CAPD.[5] At the Toronto Western Hospital, the overall survival of the insulin-dependent (Type I) diabetics on CAPD is 89%, 65%, 58% and 58% at the end of 1, 2, 3 and 4 years, compared with 92%, 81%, 72% and 66% for non-diabetics.

In a previous study,[6] we demonstrated that patients with pre-existing cardiovascular disease have a lower survival than those who do not have cardiovascular disease at the start of CAPD.

In a selected group of low-risk patients (i.e. those aged between 20 and 60 without co-existing systemic diseases such as diabetes mellitus, vasculitis, scleroderma, amyloidosis and multiple myeloma and without pre-existing cardiovascular complications such as angina pectoris, myocardial infarction and hypertensive cardiomyopathy), we found a 100% survival at the end of 4 years on CAPD (Fig 2).

CAPD AND KIDNEY TRANSPLANTATION

Among CAPD patients awaiting transplantation, the principal risk factors which are related to peritoneal dialysis and may affect the outcome are peritonitis, perforation of peritoneal cavity during the procedure and catheter skin exit infections. Patient and graft survival are comparable in patients who were maintained on haemodialysis or peritoneal dialysis before transplantation.[7] Problems with the catheter and exit-site are uncommon and can be managed

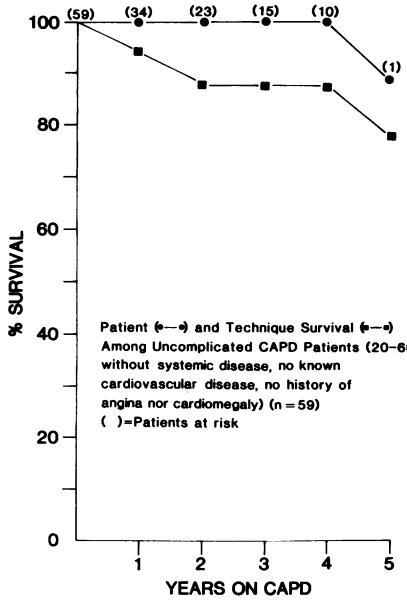

Fig. 2. Survival of low risk patients on CAPD (See text for the definition of 'low-risk')

without complications.[8] If peritonitis develops in the post-operative period, it can be treated easily with antibiotics and early removal of the catheter. Immunosuppressive therapy does not increase the incidence and severity of peritonitis.

Patients in whom renal transplantation fails can be treated again by CAPD. Of 22 such patients who returned to our CAPD programme, survival was 84% at the end of the first year, and 73% at the end of the second year. These figures are slightly lower than those for the general CAPD population, probably because these patients had multiple problems, such as rejection, intensive treatment with cytotoxic drugs and repeated episodes of severe infection. These patients did not have a higher incidence of peritonitis than the general CAPD population.

QUALITY OF LIFE

It is difficult to measure quality of life. Sometimes it can only be inferred from the patient's activity level, employment status, sexual activity and relationship with the other family members.

A review of the level of rehabilitation among the patients in our programme at the end of 1983 (Table II), showed that 38% were working full-time — either in employment or as homemakers with normal activity. The level of the rehabilitation in work scale is low because a large proportion of our patients were over the retirement age; this result is not significantly different from that reported for a large population of ESRD patients on haemodialysis.[9] Fifty-four per cent of our patients claimed that their daily activity was normal. Among the 59 young

TABLE II

Rehabilitation of 86 patients on Toronto Western Hospital CAPD programme on 31 December, 1983

Occupational status		*(%)*	*Daily activity*		*(%)*
Full-time	12	(14)	Normal	54	(63)
Part-time	0		Restricted	26	
Sick leave	6		Requires care	5	
Homemaker (normal activity)	21	(24)	Confined to bed	0	
Homemaker (restricted)	10				
Unemployed	11				
Retired (normal activity)	11	(13)			
Retired (restricted)	14				

patients without systemic complications (as defined previously), 64% were fully rehabilitated and 85% had normal daily activities.

In a retrospective multicentre survey of the demography, physical activity and employment status of CAPD and haemodialysis patients carried out by questionnaires, Fragola et al[10] found that 68% of the non-diabetic and 48% of the diabetic CAPD patients were capable of greater activities than self-care. Corresponding figures for haemodialysis patients were 59% and 23% respectively. These differences were statistically significant.

Churchill et al tried a new approach in measuring the quality of life in dialysis and transplant patients which they have called the 'time trade-off' technique.[11] The patients were given a hypothetical choice: they could either continue in their present state of health with its physical, emotional and social limitations for a lifetime (t) (determined from actuarial data) or they could choose a shorter time (x) in a state of full health except for the normal ageing process. The value (x/t) is an index of the health state or the perceived quality of life for the individual. They found that the mean values for hospital-based haemodialysis, CAPD and transplantation patients were 0.57, 0.57 and 0.80 respectively.

Sexual function

Sexual dysfunction is common in patients with chronic renal failure and those on dialysis.[12] The patient and the partner are under constant physical and psychological stress. They have to adjust every aspect of daily living to the restraint of dialysis. The patient's illness may force the spouse to change roles in earning income, assuming responsibility for housework and raising of the family. This change produces great stress, and frequently the patient may not be able to accept the new role. In addition to these psychological factors, a concomitant abnormal metabolic and hormonal status may produce a sexual dysfunction. Abnormal sex hormone homeostasis has been implicated in patients with renal failure.[13-15] Sexual dysfunction has been attributed to impaired pituitary function with inadequate levels of FSH and LH, high level of prolactin and low level of zinc.[16, 17] In addition, CAPD patients may find the body image distorted by the presence of the catheter, the empty bag and the dialysis solution in the abdomen, and this may impair libido further. Burton et al[18] showed that substantial numbers of dialysis patients, whether on haemodialysis or CAPD, reported marriage strain, sexual dysfunction, and altered perceptions of sexual identity and attractiveness. However, patients undergoing haemodialysis complained significantly more often about all four kinds of marital-sexual stress than did patients on CAPD.

Resumption of menses

Most women do not menstruate while on maintenance haemodialysis. Galler et al[19] reported that 86% of those on CAPD and only 25% of those on haemodialysis have regular menses. Frequently, amenorrhoeic females on haemodialysis resume menstruation after being started on CAPD. Even though the ovulatory cycle is still rare, resumption of menstruation often has a beneficial psychological effect on women with renal disease.

Pregnancy is still a rare event among women on dialysis and successful pregnancies with a live birth are even more unlikely. Kioko et al[20] described a successful pregnancy in a 26-year-old woman with advanced diabetic nephropathy treated with CAPD. The pregnancy was carried to 34 weeks and an infant

of 1.7 kg was delivered by Caesarean section. Two other women on CAPD became pregnant,[21, 22] but both ended in spontaneous abortion at 13 and 32 weeks.

CAPD IN CHILDREN WITH ESRD

CAPD has made an important contribution to the treatment of children with ESRD, especially the very small ones.[23]

Baum et al[24] compared two groups of children, one treated by CAPD and the other by haemodialysis. In the children on CAPD, protein and caloric intakes were higher and the growth rate was slightly faster but the difference did not reach statistical significance. CAPD treatment was more cost-effective than haemodialysis. In another report,[25] Balfe reported that children treated by CAPD grew faster than those treated by haemodialysis, although the growth was still not as good as in children with successful renal transplants. It appears that children with end-stage renal failure would have a growth rate which would approach normal, if one controlled hyperparathyroidism and gave optimal nutrition. Kohaut,[26] who described significant catch-up growth in children treated with CAPD, stressed the importance of careful and intensive management of hyperparathyroidism and close attention to nutritional needs; the children in the latter study ingested about 2g of protein/kg of bodyweight. Thus CAPD makes it possible to liberalise the diet and fluid intake in a group of patients who are particularly difficult to manage.

BIOCHEMICAL CONTROL

In most individuals CAPD with eight litres per day (i.e. 4 × 2 litre exchanges) stabilises the biochemical abnormalities (Table III). The following observations about serum potassium and phosphorus may be of particular interest:

Potassium: Each day CAPD removes approximately 25 to 35 mmol of potassium, and some CAPD patients become hypokalaemic despite a liberal potassium intake (60-80 mmol/day). This may be due to increased potassium loss from the gastrointestinal tract,[27] or intracellular accumulation of this ion associated with absorption of glucose from the dialysate or urinary loss, e.g. in a patient receiving large doses of furosemide.

Phosphorus: CAPD alone does not remove enough phosphorus to keep the serum phosphorus at normal levels. Most patients also require a phosphorus-restricted diet and/or a phosphorus binder but in a dose smaller than that required in haemodialysis. Aluminum binders are unpalatable, may aggravate constipation and even precipitate diverticulitis, and may contribute to the development of osteomalacia and dialysis dementia. The risk of these complications can be minimised by using a magnesium-free dialysate in combination with phosphorus binders containing a mixture of magnesium hydroxide and aluminium hydroxide. This mixture. which has a mild laxative effect, binds phosphorus with a lower dose of aluminium hydroxide and is more palatable.

FLUID INTAKE

One can be more liberal with fluid intake in CAPD than in haemodialysis because ultrafiltration is continuous and thirst is decreased. Large volumes of ultrafiltrate can be removed by the use of hypertonic (4.25% dextrose) exchanges — 600-800 ml/exchange. Recently, however, we have been advising our patients

TABLE III

The blood biochemical values of patients on four × 2 litre exchanges/day, after one year of CAPD treatment

	Four bag days
	Mean ± std dev.
Blood urea nitrogen (mg%)	54.1 ± 16.6
Creatinine (mg%)	11.5 ± 1.5
Calcium (mg%)	9.3 ± 0.64
Phosphorus (mg%)	4.2 ± 0.75
Uric acid mg%	6.9 ± 1.03
Total protein gm%	6.3 ± 0.93
Albumin gm%	3.2 ± 0.44
Potassium mEq/l	4.0 ± 0.59
Cholesterol mg%	237.2 ± 80.7
Triglycerides mg%	299.3 ± 134.2
Haemoglobin gm%	9.3 ± 1.9
Platelets (x 100/mm^3)	501.3 ± 106.41

against the liberal use of water because frequent hypertonic exchanges lead to increased glucose absorption with all its consequences — lipid abnormalities, obesity and possibly damage to the peritoneum.

CAPD AND URAEMIC COMPLICATIONS

Control of hypertension

Blood pressure is controlled easily in patients on CAPD and usually returns to normal during the first few weeks. We measured blood pressure in 197 patients, before and after CAPD. Before starting CAPD, 77% of the patients had hypertension, defined as a systolic >160 mmHg and/or a diastolic >90 mmHg; all were on antihypertensive medication and only 23% had a normal blood pressure. While on CAPD, 74% of those who initially were hypertensive became normotensive and required no further medication. Another 20% had normal blood pressure on antihypertensive medication, but the dosage was smaller than before. Of the patients who initially were hypertensive, 6% remained hypertensive. Because of the ease with which hypertension is brought under control occasionally we have started CAPD on patients suffering from intractable hypertension, even though their renal failure had not advanced to the point where they required dialysis.

Leenen et al[28] studied with serial M mode echocardiography 17 CAPD patients all of whom had a history of hypertension and had echocardiographic evidence of increased LV (left-ventricular) mass related to both concentric and eccentric hypertrophy. On CAPD the blood pressure returned to normal consistently. In 14 of 17 patients, left-ventricular mass decreased as a result of reduction in both LV wall thickness and LV dimension. Repeat echocardiography showed improvement in three of four patients who initially had impaired LV function. These workers concluded that CAPD improves LV hypertrophy by normalising pressure and volume overload of the left ventricle.

Control of anaemia

The average haematocrit is 30-35% and the average haemoglobin is about 9-10 g/dl in the CAPD patients. These patients require transfusions and anabolic steroids less frequently than those on haemodialysis.[29] Frequently it has been observed that haemoglobin and haematocrit increase in patients transferred from haemodialysis to CAPD.[30]

In 34 patients on CAPD, DePaepe et al[31] found a significant increase in haemoglobin and haematocrit in the first 6 months of CAPD. The elevated haematocrit represents a combination of true increase in red cell mass and a decrease in plasma volume. The serum PTH and ferritin remained unchanged. Zappacosta also found a significant increase in haematocrit in four of nine CAPD patients,[32] and it appears that those who respond to CAPD are those who have high erythropoietin levels. Three of the four responders had polycystic kidney disease.

As yet we have no explanation for the improvement of erythropoiesis in patients on CAPD. Lamperi et al confirmed the improved erythropoiesis by *in vitro* studies of the colony-formation capacity of the bone marrow cells but found no correlation between the rise in haematocrit levels and the serum erythropoietin levels.[33] They suggested that the improved erythropoiesis results from the removal by CAPD of toxic factor(s), which suppress bone marrow. Hefti et al, who studied red cell survival in 11 CAPD patients, found that the reduction in red cell survival still persisted — the mean 51 Cr red cell half-life was 20 days.[34]

Pericarditis

The incidence of pericarditis in patients with ERSD is reported to be 32%-41%,[35,36] but, with earlier and more effective dialysis, uraemic pericarditis can be prevented. The incidence of uraemic pericarditis among patients on chronic haemodialysis varies from 10% to 18%.[37,38] Pericarditis is an infrequent complication among our CAPD patients. Since the beginning of our programme, we have encountered only 9 episodes of pericarditis among 257 patients. None of these developed tamponade; one developed pericarditis following a reactivation of systemic lupus erythematosus.

Neuropathy

Neuropathy was identified as a complication of advanced renal failure in 1961,[39] but its cause remains an enigma. Frequently it has been attributed to an accumulation of uraemic toxins of middle molecular size.[40] Initially we hoped that CAPD patients might have a lower incidence and slower progression of uraemic neuropathy than those on haemodialysis or intermittent PD because it achieves a better clearance of middle molecules.

We have studied the electrophysiological parameters in 23 non-diabetics and 6 diabetics who have been on CAPD for three years or more. Figs 3a and 3b show the sequential motor and sensory conduction velocities in these patients. Linear regression analysis of nerve conduction velocity as a function of time showed no significant change following dialysis. Motor nerve conduction velocities in diabetic patients also remained unchanged. These data suggest that peripheral neuropathy does not progress in patients on CAPD for prolonged periods. Contrary to our findings, Lindholm et al[41] showed that peripheral neuropathy may worsen during CAPD. However, the presence in their study of a marked predominance of males may have influenced their results, because men are more prone to uraemic neuropathy than women.[42]

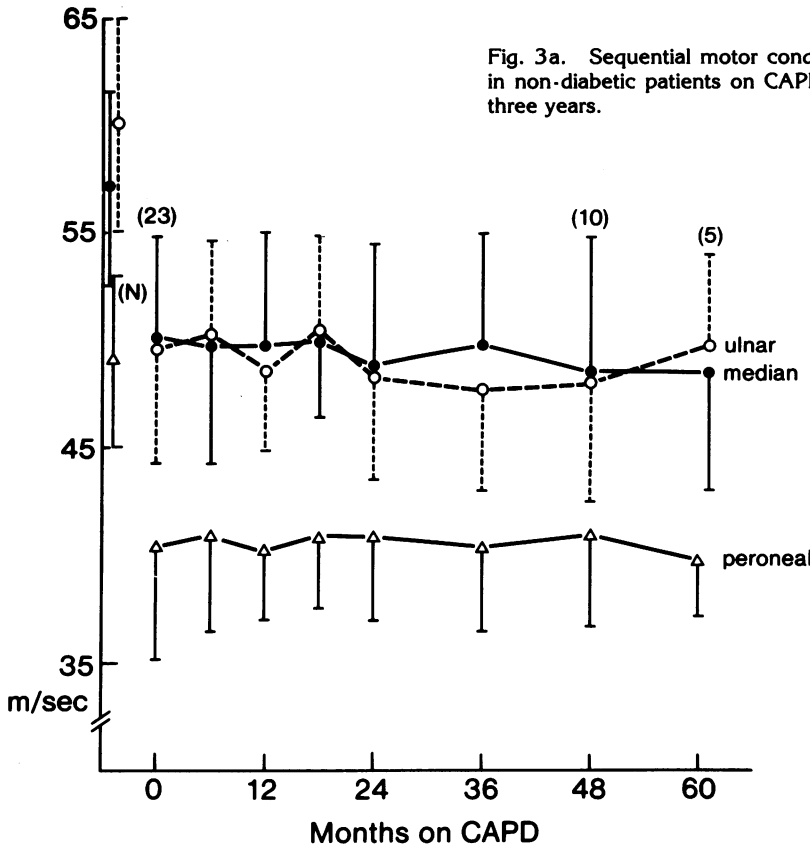

Fig. 3a. Sequential motor conduction velocities in non-diabetic patients on CAPD for more than three years.

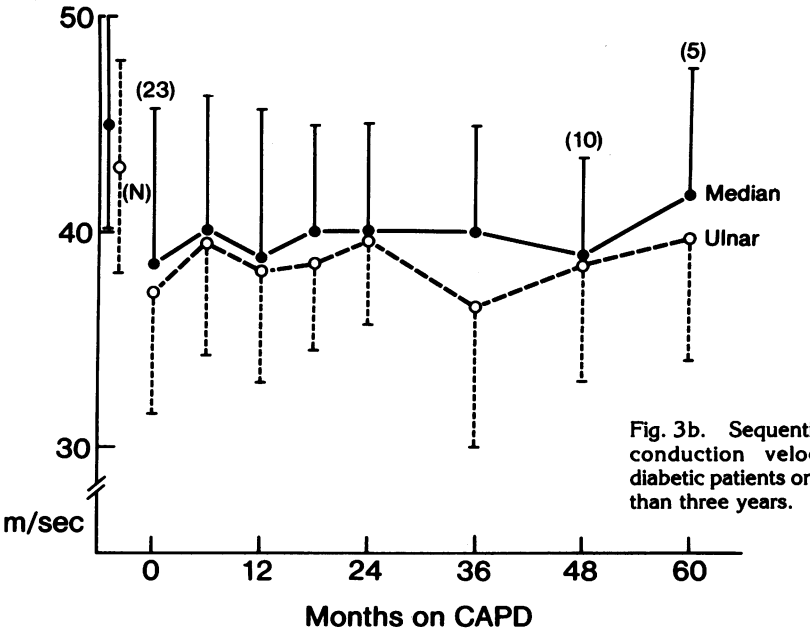

Fig. 3b. Sequential sensory nerve conduction velocities in non-diabetic patients on CAPD for more than three years.

Cognitive function

A large proportion of patients with advanced renal failure have a significant degree of cognitive dysfunction which is attributed to neurotoxicity before treatment. Kenny[43] developed an 'impairment index' to assess cognitive dysfunction in individual CAPD patients. This index, which ranges from 0.0 (no impairment) to 1.0 (severe impairment), is calculated on the basis of eight psychometric tests. He studied 46 patients over 12 months of CAPD treatment. In the beginning, only 37% of them had normal cognitive function (score 0.0 – 0.2), whereas 22.7% had markedly impaired function (score > 5.0). At the end of one year, 59% had normal cognitive function and the proportion of those with markedly impaired scores dropped to 13%. The population of non-impaired patients increases up to 70% after treatment for two years or more.

Renal osteodystrophy

Renal osteodystrophy is a major complication of long-term dialysis. With the better control of serum phosphorus, one would expect improvement in the course of renal osteodystrophy in CAPD patients. So far the results have been conflicting. Tielemans et al[44] found that osteitis fibrosa progressed in 15 patients who were on CAPD for 7 to 28 months. Teitelbaum et al[45] studied six CAPD patients by repeated bone biopsies and found that osteomalacia improved whereas the osteitis fibrosa worsened. Gokal et al[46] studied 40 CAPD patients dialysed with a dialysate calcium of 7 mg/dl and found improvement of both osteomalacia and osteitis fibrosa during the first year. The parathyroid hormone level declined in three-quarters of the patients. Digenis et al[47] reviewed the radiological evidence of renal osteodystrophy in 27 patients who had been on CAPD for three years or more. According to the radiological findings at the beginning of the treatment, they divided these 27 patients (10 males and 17 females) into two groups: Group A (10 patients) included those who had no subperiosteal resorption, and group B (17 patients) those with increased subperiosteal resorption. In group A, the radiological findings remained normal in 8 and progressed in 2. In group B, subperiosteal resorption remained unchanged or progressed in 14, while it improved in the other 3. Plasma PTH levels paralleled the radiological changes. Of the 27, 7 developed spontaneous fractures which, however, healed with callus formation. Thus secondary hyperparathyroidism persists in patients on long-term CAPD in our experience; this may be due to a low dialysate calcium and low oral calcium intake.

Abnormalities in lipid metabolism

Almost one-half of those on CAPD develop hypertriglyceridaemia, which has been attributed to the large load of glucose (150-200 g) absorbed daily from the dialysate.

In a prospective study of the effect of three to six months on CAPD[48] on serum lipids, we found that patients with high triglycerides before starting CAPD continued to have high levels, which, in some, rose even further. The VLDL cholesterol also increased whereas HDL cholesterol did not change. Serum triglyceride and cholesterol levels remained normal in those who had normal lipid profiles at the start of CAPD. After three to six months of CAPD, the HDL cholesterol increased significantly in this group. Lindholm et al[49] also found that the serum lipids remained normal in a large proportion of their CAPD patients.

Hypotension and peripheral vascular disease

CAPD controls blood pressure so effectively that occasionally these patients develop orthostatic hypotension. Brown et al[50] reported that a drop in the systemic blood pressure and in the already impaired perfusion of the ischemic limbs could exacerbate symptoms of peripheral vascular disease. It may be necessary to remove patients from CAPD and allow their blood pressure to increase so as to alleviate the symptoms of peripheral vascular disease. Leenen et al[51] studied 5 symptomatic, hypotensive patients before and after oral salt loading, during which they did not allow a concomitant increase of body weight. The patients received between 85 and 170 mmol of sodium per day in addition to the original daily intake. Salt-loading lasted two to three weeks. Supine blood pressure increased markedly after salt loading, from 94/67 mmHg to 121/78 mmHg, and the symptoms of orthostatic hypotension disappeared. Salt-loading appears to confer its benefits by increasing extracellular fluid volume and sympathetic tone, as assessed by plasma norepinephrine levels and the pressor responsiveness to norepinephrine.

Causes of death

Of 257 patients on our CAPD programme, 42 had died. Sixteen died of cardiovascular causes and 10 died suddenly. We believe that most of the latter died of cardiac causes, because most of them had evidence of cardiac abnormalities on routine tests before death and none had electrolyte disturbances. Thus cardiovascular deaths accounted for more than one-half of the deaths on CAPD. Seven patients died of peritonitis. They either had a *Staphylococcus aureus* infection or faecal peritonitis due to perforation of viscus. The remaining 9 deaths were due to causes such as pancreatitis, withdrawal from dialysis and malignancies.

COMPARISON OF THE COSTS OF THE VARIOUS MODES OF DIALYSIS

The most expensive part of any dialysis therapy is the services of medical personnel and the provision of equipment. CAPD achieves the most effective reduction in labour costs because the patient carries out the entire procedure. This mode requires only minimal equipment. The Toronto ESRD Task Force has calculated that (per patient year) CAPD costs much less than centre peritoneal dialysis and haemodialysis.[52] It is also cheaper than home dialysis.[52, 53] In Toronto (1983) CAPD costs Can $15,000 per patient year compared with Can $27,000 for centre haemodialysis and Can $18,000 for home haemodialysis.

Most centres refer patients of advanced age and those with cardiovascular diseases to the CAPD programme because it achieves a stable haemodynamic and biochemical condition. These patients tend to have multiple medical problems and hence to require frequent admissions which invariably add to the total cost of CAPD.

Even though CAPD is less expensive than hospital or facility based haemodialysis, it still remains relatively expensive and we should continue our efforts to lower the cost of dialysis solutions — the main expense. We can reduce the cost of CAPD by decreasing the frequency of exchanges from four to three per day, using either 2 or 3 litre bags. This modification would lower the total cost of dialysis solution but also would reduce the cost of peritonitis treatment, because the frequency of

peritonitis is much lower in those using three exchanges per day.[54] At a time when economic resources are limited, reducing the cost of renal replacement therapy to a minimum will enable physicians to treat more patients with end-stage renal failure.

CONCLUSION

As this paper explains, CAPD provides adequate removal of metabolic wastes, ameliorates some of the common long-term complications and restores disturbed physiology towards normal in end-stage renal failure. Thus CAPD is an important treatment for patients with end-stage renal disease. While it is the treatment of choice for some patients it may not be tolerated by others who then will be maintained by haemodialysis. Centres which cannot provide both haemodialysis and CAPD with equally high standards function under a considerable handicap.

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High cost dialysis and transplantation — dilemmas for nephrologists and nations

A J Wing

SUMMARY

The linked successes of dialysis and transplantation pose dilemmas for nephrologists struggling to meet the clinical need and for health care planners wondering where to find the resources required. The low rate of acceptance of new patients in the UK compares unfavourably with the service given in other countries. Successful rationing is achieved by a sparse distribution of centres and of specialists and operates through a low rate of referral of patients to nephrologists. Political initiative is beginning to emerge to redress the underprovision of facilities by setting realistic targets before regional health authorities.

INTRODUCTION: DILEMMAS POSED BY SUCCESS

It is the success of dialysis and kidney transplantation during the past 25 years which now poses dilemmas for nephrologists and nations. Renal replacement therapy (RRT) prolongs life for patients who would otherwise die of end-stage renal failure (ESRF). This life is of a reasonable quality and patients have an expectation that RRT will be offered to them if they need it.

The modern treatment of ESRF consists of complementary dialysis and transplantation. Most renal units have available both haemodialysis and peritoneal dialysis. Haemodialysis is carried out both in the hospital unit and by patients in their own homes. Peritoneal dialysis when used for long-term therapy is usually administered as continuous ambulatory peritoneal dialysis (CAPD). Individual patients may experience all these methods of therapy at various times in their careers on RRT. The treatments are thus termed 'integrated'. Reasons for choice of one therapy at a particular time include patient preference as well as medical and domestic considerations. Inevitably, economic factors enter into such deliberations and it is seldom possible to take these decisions for an individual without weighing their effect on the group of patients in a programme.

This paper presents data from the patient registry organised by the European Dialysis and Transplant Association-European Renal Association (EDTA-ERA) to illustrate the differences in provision of RRT in various European countries.[1] Mechanisms which ration high cost medical care in the United Kingdom have been investigated.[2] Ethical dilemmas for governments which provide health care and for doctors — in this case nephrologists — who dispense it are becoming ever more painful.

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THE COST OF DIALYSIS AND TRANSPLANTATION

RRT is expensive. The price is excessive for poor nations and not without embarrassment for the wealthier. It is a popular misconception that the cost of treatment is the price of a kidney machine. The capital cost of a machine which manufactures dialysis fluid and monitors the dialysis procedure is around £5,000 to £6,000. The revenue implications in terms of consumables — disposable dialysers, blood lines, dressings and drugs — amount to a further £2,000 to £3,000 per annum. In addition there are the overheads of the renal unit and its staff.

Overall costs of the different methods of dialysis and of transplantation in its first and subsequent years are given in Table I.[3] Successful transplantation is obviously the 'best buy'. From this the economic importance of cadaver procurement is evident. However, nearly all patients experience a short or long period on dialysis while waiting for a suitable graft, and dialysis should also be provided for patients whose grafts have failed. A graft carries greater risks for certain patients but risks are diminishing as results improve and its lower cost will encourage doctors to offer transplantation to a wider spectrum of patients with ESRF.

TABLE I

Costs of various methods of RRT (Mancini, 1984[3])

	£
Hospital haemodialysis	10,650 — 12,300
Home haemodialysis	7,250 — 7,850
CAPD	6,050 — 6,950
Successful transplantation:	
First year	5,600 — 6,400
Subsequent years	1,600 — 1,850

Mean survival exceeds ten years. A clinical decision to admit a patient to an integrated treatment programme therefore obligates approximately £100,000 at present-day prices. Because of good results, the stock of patients in a programme may be expected to continue rising for many years before it reaches a plateau. In no country has the number of patients alive on RRT yet levelled off. It must therefore be predicted that the economic burden in terms of personnel and plant will continue to increase.

The treatment of ESRF began in the 1960s, a period of expanding economies when even the moon was coming within the reach of mankind. In the United Kingdom, central funding was provided by the Department of Health and Social Security (DHSS) to get the programme off the ground. The geographical distribution of centres matched the major concentrations of populations and was a fine advertisement for a nationalised organisation moving in a co-ordinated and imaginative way to bring a new advance in therapy to the population it served. However, health authorities have since learnt that capital grants without an annual increment to meet the revenue implications are often less than welcome.

The two decades of RRT have witnessed increasing concern at the cost of high technology medicine and the growing proportions of gross national product consumed by health care. Godber has discussed the need to strike a balance in health expenditure between therapy, prevention and support.[4] He advocated compromise to provide the most for the most and not everything for a few. The small number of patients with ESRF whose treatment is readily costed are beginning to be seen as consuming more than their fair share of medical resources. Yet how fair was it that their lives should be held ransom by kidney disease which can only be treated by continuing substitution therapy rather than pneumonia cured with a week's antibiotics or a perforated peptic ulcer corrected by a single operation?

The conflicting claims of preventive measures and transplant surgery are not infrequently the cause of public debate and were the subject of an interesting correspondence in *The Times* in 1979. I have kept this correspondence on my files and while re-reading it recently found my attention riveted on one letter: " **** is entitled to write at length about prevention being better than cure in medicine as in other things. But I trust he will not overlook a substantial number of people for whom prevention will come too late . . . . " The reason why this letter so caught my eye was the name of the author: unknown to me when he wrote it five years before, he had in recent weeks become my patient and commenced dialysis.

NATIONAL DIFFERENCES IN THE PROVISION OF RRT

The EDTA-ERA Registry has a computer file of almost 150,000 patient records going back to the beginning of dialysis and transplantation in Europe. It is a uniquely comprehensive record of medical endeavour. Tables II and III and Figures 1-5 are derived from this data-base.

TABLE II

Number of centres and of patients per million population (pmp) on 31 December 1983 in various European countries

	Pop. (millions)	*Known centres pmp*	*Registerd patients pmp*			
			Haemo-dialysis	*Peritoneal dialysis*	*Graft*	*TOTAL*
Benelux*	24.2	4.5	161	14	62	237
Fed Rep Germany	61.2	4.9	221	6	31	258
France	53.4	3.9	202	17	36	255
German Dem Rep	16.8	3.1	73	1	24	98
Irish Republic	3.3	1.5	51	11	56	119
Israel	3.8	6.8	220	24	57	301
Scandinavia**	22.5	3.9	69	21	98	188
Spain	37.0	5.0	190	15	30	236
Switzerland	6.5	5.2	166	28	72	267
United Kingdom	55.9	1.1	62	23	68	153
Yugoslavia	22.1	3.4	95	1	6	103

*Belgium, Luxembourg and The Netherlands.
**Denmark, Finland, Iceland, Norway and Sweden.

Table II shows the number of centres providing treatment and the cumulative stock of patients in each country, each figure being given per million of population to facilitate comparisons. The number of centres is a constraint on patient numbers and the low number of patients in the United Kingdom, only 153 patients per million population (pmp), is obviously related to the restricted number of centres, 1.1 pmp. Average work load per UK centre is thus much greater than in the average European centre indicating that British centres tend to be larger and probably more cost-effective. The stock of patients describes the current work load and the staff and facilities are related to this.

The opportunity for a new patient to obtain treatment is determined by the rate of acceptance of new cases and Table III shows the rates for patients aged under and over 65 in different countries. The low acceptance rate in the UK particularly disadvantages patients aged more than 65.

TABLE III

Rate of acceptance of new patients of all ages and over 65 per million population in 1983 in various European countries

Country	*New patients all ages pmp*	*New patients >65 pmp*
Benelux	52	11
Fed Rep Germany	56	12
France	44	10
German Dem Rep	28	1
Irish Republic	24	1
Israel	67	13
Scandinavia	52	8
Spain	61	7
Switzerland	55	10
United Kingdom	33	3
Yugoslavia	32	2

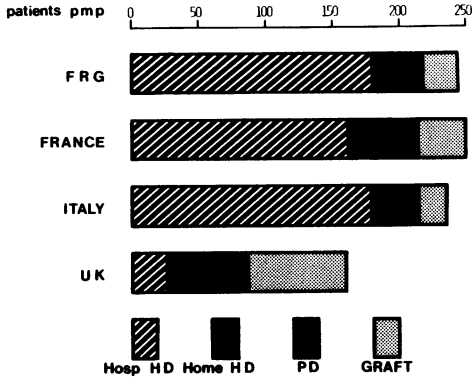

Fig 1. Number of patients per million population on RRT in four large European countries according to method of treatment.

Not only do the constraints operating in the UK limit patient numbers, they also have a marked effect on the distribution of patients between different treatment modalities (Fig 1). Because of the limitation of hospital stations in the UK, patients who can only be treated by hospital haemodialysis (Fig 2) are accepted with reluctance because they might block hospital facilities which are the corridor to home haemodialysis, CAPD, and transplantation. A pattern of selection has emerged in which patients who are capable of independent treatment are accepted

and those who are not are excluded. However, RRT in elderly and dependent patients has been shown to result in a satisfactory quality of life and worthwhile survival. Their exclusion from therapy in the UK cannot be justified on clinical grounds and can only be attributed to value judgements forced on doctors by the economic constraints under which they work.

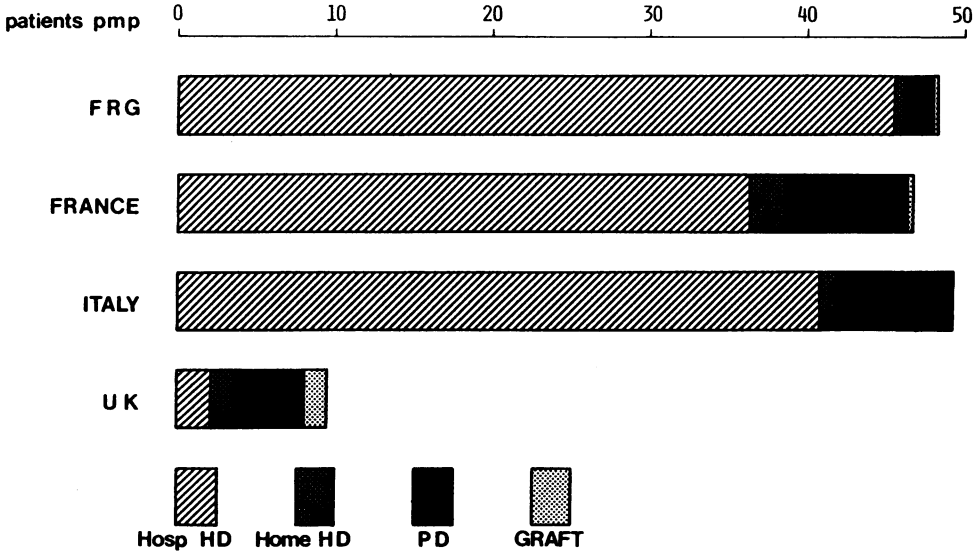

Fig 2. Number of patients aged over 65 per million population on RRT in four large European countries according to method of treatment.

Figure 3 shows how the numbers of patients have accumulated year by year on different methods of therapy in the UK. Figure 4 compares the achievements in Northern Ireland. The population of 1.5 million in Northern Ireland is served by

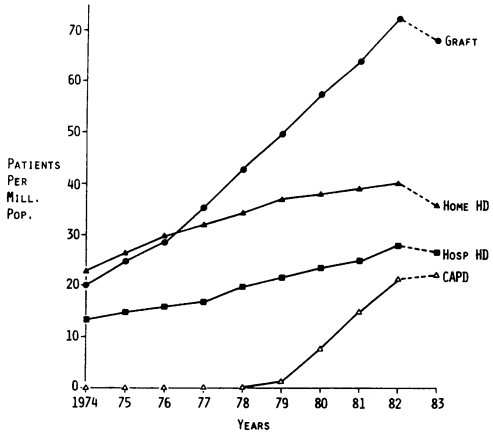

Fig 3. Cumulative stock of patients on 31 December 1974 – 1983 according to method of treatment in the UK. (Figures for 1983 incomplete).

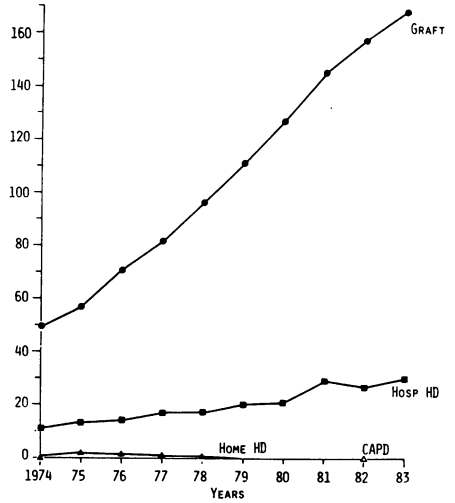

Fig 4. Cumulative stock of patients on 31 December 1974 – 1983 according to method of treatment in Northern Ireland.

the single unit whose 25th anniversary is celebrated by this Symposium. The excellent results of transplantation[5] have made a vital contribution here over the years. Unlike practice in the rest of the UK, CAPD has not yet been used extensively to help out hard-pressed hospital haemodialysis.

RATIONING OF RRT IN THE UK

All British nephrologists testify to the pressure under which their units are operating but it seems that they very seldom have to turn away patients whom they consider suitable for treatment and certainly never at the anticipated rate of 25 patients per unit per year. Is the need for treatment less in the UK? There is no evidence that the incidence of ESRF is lower in the UK than in other European countries. Then, where are the untreated patients? What is happening to them.[6]

The answer lies in the mechanism of access to specialised services under the National Health Service. The patient cannot refer himself directly to the specialist who he deems will help him most. Hospital specialists only see patients at the request of their general practitioners. It is therefore possible that treatment rate is controlled by the physician who first diagnoses ESRF when he decides whether or not to refer a patient. The 'gatekeeper' could be the primary care physician but it seems more likely that it will be the consultant in the hospital where the diagnosis is made. Chronic renal failure requires only a biochemical test of the blood to make the diagnosis but before that is done it can masquerade under many clinical presentations since uraemia causes diverse symptoms. Moreover, approximately one-third of all patients with ESRF have followed an insidious course and present as acute uraemic emergencies, often requiring dialysis within a few days if not hours. Because of the low ratio of renal units to population in the UK, the patient has a four-out-of-five chance of being diagnosed in a district general hospital without a nephrologist or a renal unit. If he is to be treated he must be referred to another hospital, perhaps 50 miles or more distant from his home.

To test this explanation for the low treatment rate of ESRF in the UK we circulated a questionnaire containing 16 brief patient histories to a random selection of general practitioners and consultant physicians and to all nephrologists in the UK.[2] The respondents were asked whether they thought each of the cases suitable for dialysis and/or transplantation. All the cases had complicating medical and domestic problems mitigating against successful good quality life on RRT. A significantly higher ($p < 0.001$) number of the 16 cases was rejected by both consultant physicians (7.4 ± 0.2) and general practitioners (6.9 ± 0.3) than by nephrologists (4.7 ± 0.3). Interestingly, the ranking of patients according to suitability produced a close correspondence between the three groups of doctors suggesting that factors other than specialist knowledge determined 'negative selection'.

The same questionnaire was also sent to colleagues in Europe and North America asking them to circulate it amongst primary care doctors and non-nephrologists. Negative selection averaged 0.3 of the 16 cases in North America, 3.6 in Western Europe and 7.5 in Eastern Europe, suggesting that decisions of British consultant physicians reflect an assessment of facilities for RRT in the UK on a par with the health services of communist countries.

Some of the unsolicited letters received with the questionnaires were particularly enlightening. Whereas we were told that in Europe and the USA a specialist nephrologist would virtually always have been consulted about the decisions, one

British consultant physician wrote: " . . . . I worked at my local renal unit in a junior capacity some years ago. I have always referred on merit and not based on what I know to be the facilities locally but I have made the value judgements as to who is meritorious myself . . . . the decision is mine rather than my local renal unit's . . . . ".

It may be thought commendable that individual doctors can shoulder such a responsibility. That they can do so at all probably owes much to the social structure of our country and the traditional paternalism of our learned professions. In the face of such a system, which patients are likely to get through to the renal unit? The young and beautiful, certainly. The articulate and aggressive, possibly. Those whose families, parents, children and friends will take up their cause. The request for a second opinion is a rarely exercised privilege under the NHS. Media publicity suggests that it should be invoked more often. [7] In the meantime, a rough and ready system of triage is at work maintaining a delicate equilibrium between clinical need and available facilities. In shielding their patients from the anguish of being turned down for treatment, NHS doctors are making decisions on out-of-date criteria. It appears likely that this mechanism for rationing the demands on high technology, high cost medicine and surgery also regulates referral in other specialities.

IMPROVING THE SERVICE FOR PATIENTS WITH ESRF

As a physician caring for patients with ESRF and because of my involvement with the EDTA-ERA Registry, I cannot do other than act as advocate for the cause of RRT in the UK. Physicians in this field have taken a great deal of trouble to catalogue their achievements and to assess the quality of life of their patients in an objective manner. The costs of treatment can be readily identified. The components of the cost-effectiveness equation are known. Other areas of high cost care will need to collect their own data.[8] The dilemmas as to which patients should be selected for treatment and how much resource should be allocated to each area will continue to be debated.

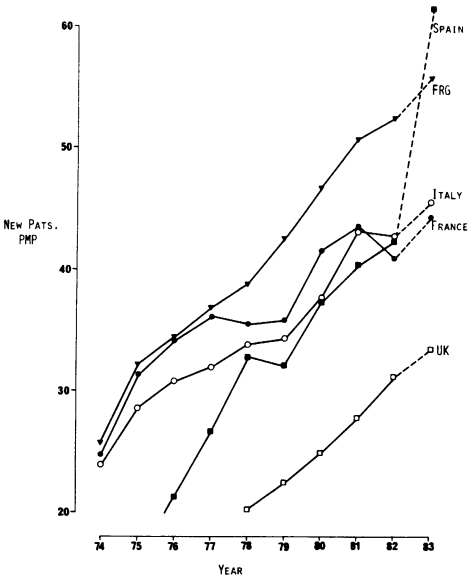

Fig 5. Increase in rate of acceptance of new patients in five European countries. (1983 figures provisional).

At the present time it is acknowledged that the rate of acceptance of new patients in the UK is too low. The DHSS is setting a target of 40 new patients per million of population 'by 1987'. The chances of therapy for a British patient would then be raised to the level of those currently available in Greece and Portugal, but would still be inferior to those in West Germany, France, Italy and Spain and many other small Western European countries. The current rate of increase in acceptance rate seems likely to realise this target, possibly without additional centres being opened (Fig 5). More imaginative is the target of the Secretary of State for

Health for Wales who has announced his intention to treat 50 patients pmp. Subsidiary renal units are being opened in Wales to accomplish this and the experiment in the Principality will be watched with great interest by the rest of the UK.

Northern Ireland has no plans, so far as I know, to augment its single renal unit which has made such a famous contribution over the last 25 years. Perhaps limited facilities could be used more intensively, by the institution of an overnight programme,[9] and perhaps the addition of CAPD to the treatment options will ease the pressures under which Dr McGeown and her staff are serving the population of Ulster. Good luck for the years ahead!

ACKNOWLEDGEMENTS

The data for Tables II and III are taken from the recent report of the EDTA-ERA Registry.[1] Figures 1, 2 and 3 have previously appeared in the UKT Service Annual Report for 1984.

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HLA matching and cadaver kidney transplantation — status 1984

Gerhard Opelz, for the Collaborative Transplant Study

SUMMARY

The effect of HLA matching on cadaver kidney graft survival was analysed in over 9000 transplants. Matching for HLA-A and -B accounted for an improvement of 8% in the one-year survival rate, matching for HLA-DR for 10%, and matching for HLA-B + DR for 19%. The matching effect of the HLA-B and HLA-DR loci was additive. Patients without pre-transplant transfusions had lower graft survival rates than transfused patients, even if their grafts were HLA matched. The highest success rate was obtained in transfused recipients who received HLA matched kidneys.

INTRODUCTION

The relevance of HLA matching, although unquestioned in the related donor situation where HLA identical siblings clearly represent an immunologically privileged category with superior graft outcome, has been difficult to establish in cadaver kidney transplantation. Conflicting reports have been published during the past 15 years with respect to matching for the HLA-A and -B antigens. The HLA-DR locus, which was introduced some five years ago, had a stronger effect according to early reports than HLA-A or -B; however, this was not substantiated in an international workshop study carried out in 1980.[1] It was recognised at that time that the technical quality of HLA-DR typing was less than satisfactory because of early difficulties with the B cell isolation technique. The picture was complicated further by a shift in transfusion policies in the late seventies and early eighties. It had become firmly established that non-transfused recipients did less well than transfused ones, and as a result the fraction of patients who received transplants without transfusion pre-treatment decreased drastically. Concurrently, typing techniques for HLA-DR were standardised and refined. The need for a re-evaluation of HLA matching in cadaver kidney transplantation became evident. In 1982, an international collaborative project was initiated, with the primary purpose of establishing on a large multicentre basis whether HLA matching had a place in modern renal transplantation. This report is an account of the early results (up to one year) that were obtained in over 9000 patients transplanted during the last two years.

METHODS

The data on which this analysis was based were gathered as part of the Collaborative Transplant Study project. Two hundred and nine transplant centres in the following cities participated: Angers, Atlanta, Barcelona, Basel, Belfast,

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Berlin-East, Berlin-West, Bern, Birmingham (Alabama), Boston, Bristol, Brooklyn, Brussels, Budapest, Buenos Aires, Cambridge, Capetown, Cardiff, Chiba, Chicago, Cincinnati, Cleveland, Cologne, Dallas, Detroit, Dublin, Ehime, Erlangen, Essen, Frankfurt, Freiburg, Fukui, Fukuoka, Geneva, Glasgow, Gothenburg, Groningen, Halifax, Halle, Hamamatsu, Hamburg, Hannover, Hartford, Heidelberg, Helsinki, Hiroshima, Homburg, Hong Kong, Houston, Innsbruck, Iowa City, Ishikawa, Kaiserslautern, Kanagawa, Kansas City, Kashihara, Kiel, Kyoto, Lausanne, Leicester, Leningrad, Leuven, Lexington, Lisbon, London, Louisville, Luebeck, Lyon, Maastricht, Madrid, Lund-Malmo, Manchester, Marburg, Melbourne, Mexico City, Milan, Minneapolis, Montpellier, Montreal, Moscow, Munster, Munich, Muroran, Nagasaki, Nancy, Nantes, Nashville, New York, Newcastle, Nice, Nijmegen, Nishinomiya, Okayama, Omaha, Osaka, Ottawa, Oxford, Paris, Perth, Phoenix, Piraeus, Portland, Porto Alegre, Prague, Quebec, Rennes, Rio de Janeiro, Rochester (Minnesota), Rochester (New York), Rome, Rostock, Saitama, San Antonio, San Francisco, Santiago, Sapporo, Seattle, Shinagawa, St Etienne, St Louis, Sydney, Szeged, Takatsuki, Tel Aviv, Thessaloniki, Tokyo, Toledo (Ohio), Torino, Toronto, Toulouse, Tubingen, Ulm, Uppsala, Valencia, Vancouver, Villejuif, Vilnius, Warsaw, Winnipeg, Zagreb, Zurich. Participation in this study was entirely voluntary. The centres agreed to provide information on all consecutive transplants only. First cadaver transplants performed between January 1982 and July 1984 were analysed. All transplants had a minimum clinical follow-up of 3 months. No exclusions were made. Graft survival rates were computed by actuarial methods. Statistical significance was calculated by weighted regression.[2]

RESULTS

The effect on graft survival of matching for HLA-A and -B is shown in Fig 1. Although there is a stepwise decrease in success rates from 0 to 4 mismatches, the difference between the best and worst match grade is a disappointing 8% at one year. Separate analysis of the HLA-A and HLA-B loci shows that there is little difference in their individual weights (Fig 2).

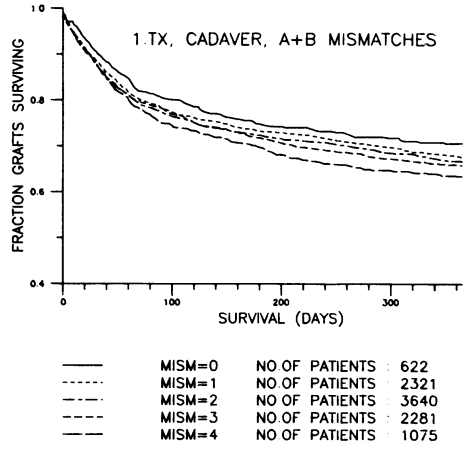

Fig. 1. Effect of matching for the HLA-A and HLA-B locus antigens on kidney graft survival. Actuarial survival rates are plotted for transplants with 0, 1, 2, 3, or 4 mismatches. Numbers of patients in each mismatch category are indicated.

Matching for HLA-DR can be seen to correlate with graft survival to about the same degree as HLA-A and -B combined (Fig 3). Although this degree of correlation is clinically useful, the discriminative power of HLA-DR alone is not as strong as one would ultimately wish to gain from tissue typing.

Both the 8th and 9th International Histocompatibility Workshop analyses showed an additive affect of HLA-B and HLA-DR on cadaver kidney transplant survival.[1,3] The current analysis clearly supports this. A difference of 19% in the one-year survival rates was found between grafts with 0 or 4 HLA-B + DR mismatches, and

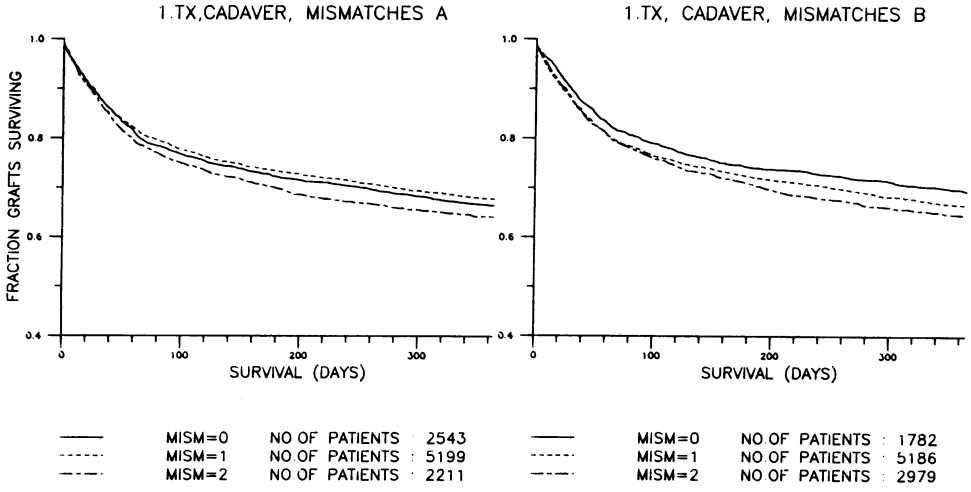

Fig. 2. Separate analysis of influence on graft survival of the HLA-A or HLA-B loci. There was no clear difference in strength between the two loci.

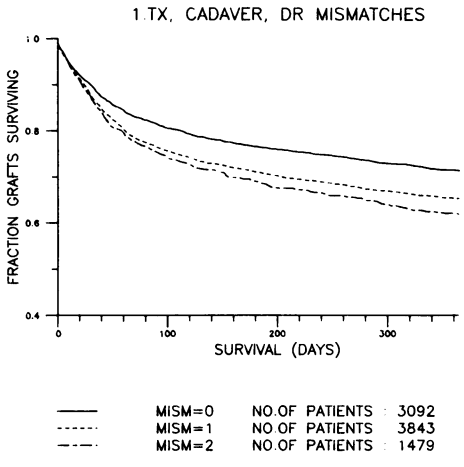

Fig. 3. Effect of HLA-DR matching on cadaver kidney graft survival. The correlation was statistically highly significant ($p < 0.0001$).

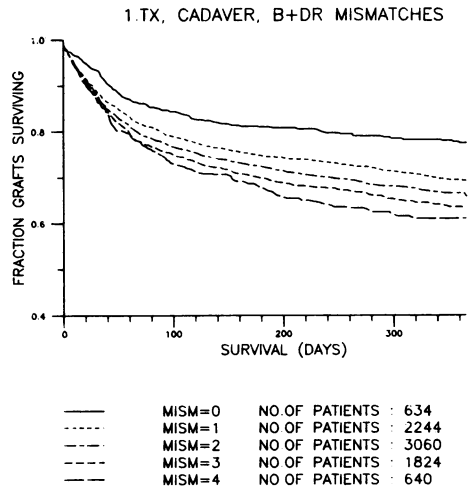

Fig. 4. Combined effect of HLA-B + DR matching on cadaver kidney graft survival. The success rate declines stepwise from 0 to 4 mismatches. Statistical significance by weighted regression: $p < 0.0001$.

the graft survival rates declined stepwise from 0 to 4 mismatches (Fig 4). No significant further improvement was achieved by including HLA-A in the analysis. The combined consideration of the three loci HLA-A + B + DR resulted in a statistically highly significant correlation with graft survival; however, the correlation was similar to that obtained with HLA-B + DR (Fig 5). Because it is desirable for logistical reasons to limit the number of loci considered in the selection process to the minimum necessary, matching for HLA-B + DR has an obvious practical advantage over HLA-A + B + DR matching.

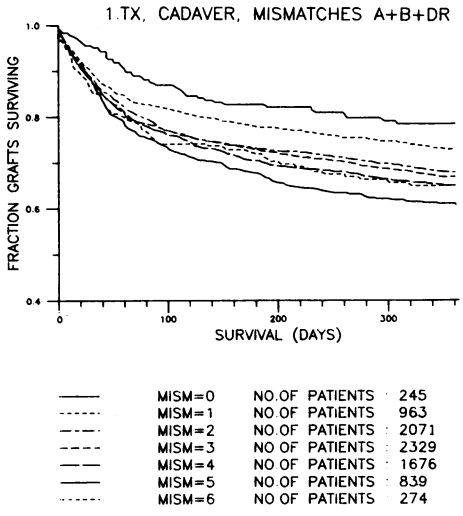

Fig. 5. Combined analysis of HLA-A, HLA-B, and HLA-DR loci. Grafts with 0 mismatches had an approximately 20% higher survival rate than grafts with 5 mismatches. The correlation was not improved compared with the analysis of HLA-B + DR.

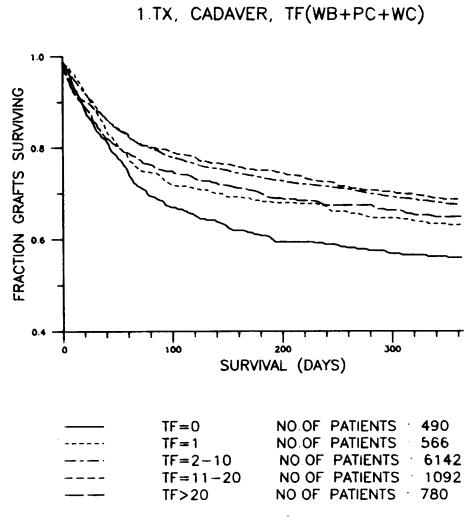

Fig. 6. Effect of pre-transplant transfusions on survival of cadaver kidney transplants. Patients without pre-transplant transfusions clearly have inferior graft outcome. 1 transfusion and >20 transfusions result in intermediately good success rates. Possibly, additional risk factors play a role in patients who received multiple transfusions.

Fig 6 shows the influence of pre-transplant transfusions on graft survival. Non-transfused recipients have the lowest success rate, patients with one or with multiple (>20) transfusions have an intermediate success rate, and the best graft outcome is observed in patients with anything from 2 to 20 pre-transplant transfusions.

A separate analysis of HLA-DR matching in transfused or non-transfused recipients is shown in Fig 7. Even though DR matching correlates with graft survival in both patient subsets, the effect of matching does not overcome the transfusion effect. In other words, well matched transplants in non-transfused recipients do not perform better than poorly matched transplants in transfused recipients. The highest success rate is obtained in transfused patients who are transplanted with HLA-DR matched kidneys (Fig 7). Unfortunately, the number of non-transfused patients was too small to allow an extension of this type of analysis to HLA-B + DR.

DISCUSSION

These preliminary results of the Collaborative Transplant Study show that HLA matching has a definite place in cadaver kidney transplantation. It remains to be seen whether the one-year results shown here will be valid also for the transplants' long-term course. Based on previous work, one can assume that this will be so.[4-6] Surely, if a method is known whereby the success rate can be improved by 20%, it must be utilised clinically.

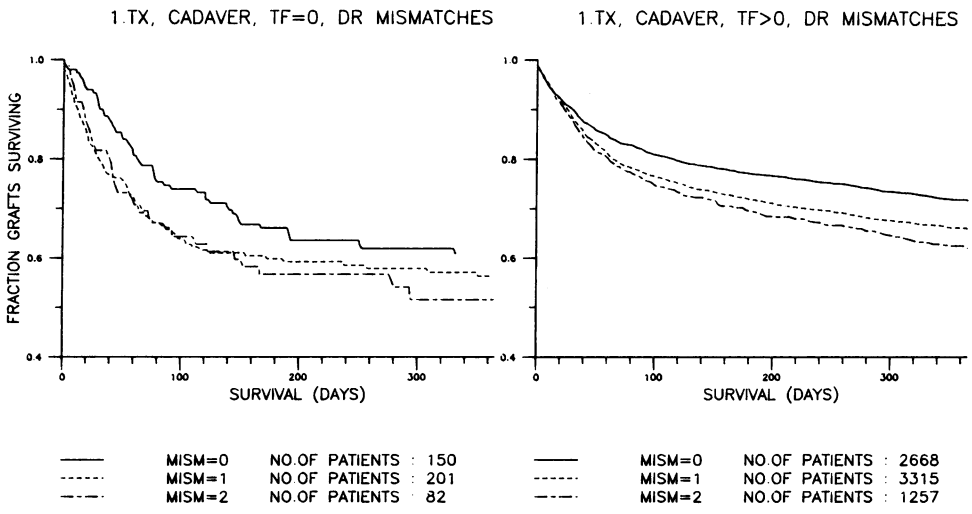

Fig. 7. Effect of HLA-DR matching in non-transfused and transfused cadaver kidney recipients. There is a matching effect in both categories; however, matched grafts in non-transfused patients are still doing worse than mismatched grants in transfused recipients.

The additive effect of the HLA-B and HLA-DR loci is confirmed in the current analysis. It appears that matching for HLA-DR alone is not sufficient for obtaining optimum results. HLA-A and -B matching is also insufficient, a fact that has long been suspected. From a logistical standpoint, HLA-B + DR matching is not as convenient as matching for HLA-DR alone; it is, however, less cumbersome than HLA-A + B matching (at least for the time being, the polymorphism of HLA-A is greater than that of HLA-DR). Therefore, it should be possible to perform many HLA-B + DR matched transplants using established organ-sharing procedures.

Our transfusion data indicate that the effect of matching can be enhanced by administering transfusions prior to transplantation. Transfused patients receiving HLA-DR matched grafts did exceedingly well, and we may anticipate that transfused HLA-B + DR matched patients will do even better.

Already, this type of analysis seems outdated in the face of cyclosporin, the new powerful immunosuppressant. First reports based on small series of patients suggest that cyclosporin may be able to overcome both the transfusion effect and the effect of HLA matching.[7,8] Quite to the contrary, preliminary data (unpublished) of the Collaborative Transplant Study indicate that there is a strong transfusion as well as HLA matching effect even with the use of cyclosporin. With the rapidly increasing numbers of transplants that are becoming available for analysis (the Collaborative Transplant Study grows at a rate of approximately 800 additional transplants per month), this new controversy is certain to be resolved within a year or two. Our experience with partially additive effects of other factors would make it seem likely that the improved success rates attributed to cyclosporin might benefit even further from the addition of transfusions and HLA matching.

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High risk factors in transplantation

Luis H Toledo-Pereyra

SUMMARY

A standardised system of assessing risk factors for renal transplant outcome and patient survival has been assessed.

INTRODUCTION

The growth of renal transplantation in the past decade and the increased amount of clinical experience in this area has allowed many transplant centres to broaden their criteria for patient selection. This has resulted in the acceptance of many patients, who were formerly considered as being 'non-ideal', into renal transplant programmes. While individual risk factors such as diabetes mellitus, cardiovascular disease, hypertension, age and race have been pointed out,[1-9] no standardised system has been employed to evaluate the contributions of the various risk factors to renal transplant outcome and patient survival.

At our centre, we have considered the combined effects of the multiple risk factors that are often simultaneously present in these patients prior to transplantation.[10] This has led to development of a scale for comparison of individual risk factors (Table I). Cumulative risk is then determined for each patient and transplant candidates are placed in an overall risk category. This allows for a more realistic pre-transplant evaluation. The present study compares the post-transplantation outcomes of two groups of high-risk renal allograft recipients at our centre receiving different immunosuppressive regimens.

PATIENT POPULATION AND IMMUNOSUPPRESSION

Group I of the study comprised 100 consecutive kidney transplants performed in 89 patients from September 1979 to November 1981. Follow-up of these patients was up to three years post-transplant. Eighty patients received primary renal transplants and 14 were transplanted with second renal allografts from cadaver donors. The remaining 6 patients received renal grafts from living related donors. Immunosuppression for patients in Group I consisted of azathioprine, prednisolone and antilymphoblast globulin (ALG). Rejection episodes were treated with ALG without increasing steroids.[11, 12]

The thirty patients in Group II were transplanted at our centre between December 1983 and August 1984. Twenty patients received primary kidney allografts, 6 patients received second renal transplants and 2 patients received a third renal graft from cadaver donors. Two patients were transplanted with kidneys from living related donors. Immunosuppression for these patients consisted of cyclosporin and prednisolone. Cyclosporin A was given pre-operatively at a dosage of 4 – 5 mg/kg (intravenously). No cyclosporin A was given during the

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TABLE I

Grading system for individual determinants contributing to cumulative risk to life of renal transplant recipients

Risk Factor	*R.R.I.**
Severe cardiac disease	0.50
Severe pulmonary disease	0.50
Disseminated collagen disease	0.50
Insulin dependent diabetes mellitus	0.40
Severe malnutrition ($\leq$50% ideal body weight)	0.40
Severe obesity ($\geq$60% ideal body weight)	0.40
Severe hypertension (diastolic pressure $\geq$110)	0.40
Oxalosis	0.40
Fabry's disease	0.40
Re-transplantation	0.40
Severe bladder disease (diversion required)	0.30
Drug addiction	0.30
Age $\geq$45 years	0.30
Liver disease	0.30
Peptic ulcer	0.30
Pancreatic disease	0.30
Controlled systemic infections	0.25
Major psychiatric disturbances	0.25
Diverticulosis	0.25
Amyloidosis	0.25
Rapid progressive glomerulonephritis	0.20
Pre-existing controlled malignancy	0.20
High level cytotoxic antibodies ($\geq$60%)	0.20
No blood transfusions	0.20
Persistent alcoholism	0.20
Membranoproliferative glomerulonephritis	0.20
Goodpasture's syndrome	0.20
Other recurrent glomerulonephritis	0.20
Focal glomerulosclerosis	0.10
Peptic ulcer disease	0.10
Heavy smoking	0.10
Endocrinopathy	0.10
Sickle cell anaemia	0.10
Hepatitis history	0.10
Poor antigen matching ($\leq$2 antigen match)	0.10

* Relative Risk Index.

first 24 hours after transplantation, an oral dose of 4–5 mg/kg was administered on post-operative days 1–3, and 6–8 mg/kg on days 4–5. The serum cyclosporin A levels were determined on days 4 and 5, and the dose was then adjusted to maintain serum levels between 100 and 200 mg/ml. After two months the dose was fixed at 4–5 mg/kg daily regardless of serum levels. Prednisolone 1 mg/kg was given immediately prior to transplant. No prednisolone was given during the first 24 hours post-operatively. Patients received prednisolone at a

dosage of 1 mg/kg on day 2, 0.75 mg/kg on days 3–5, 0.5 mg/kg on days 5–7, and were maintained at this level until discharge. Within two weeks post-transplantation, prednisolone was tapered to 20 mg daily and decreased to 5–7.5 mg daily within 3 months after transplant. Some patients were later completely removed from prednisolone. Rejection was treated with methyl-prednisolone sodium succinate, 250 mg administered intravenously every 8–12 hours for 3 days. Occasionally, antilymphocytic globulin was used to treat rejection when no response to methylprednisolone was obtained.

ANALYSIS OF RISK

Each patient in Groups I and II was evaluated to determine his or her cumulative risk prior to transplantation. Each individual risk factor was weighted as in Table I and a final risk index was calculated by adding these together. Patients with a risk index $< .6$ were considered to be good risk candidates for transplantation. Risk indices $.6 \leq x \leq .9$ were considered to be at high risk. The very high risk category included cumulative indices in the $.9 < x \leq 1.1$ range. Extremely high risk was indicated by indices > 1.1.

RESULTS

Table II compared the 6 months actuarial patient survival for each risk category in each of the groups. Survival was observed to decrease as the cumulative risk to life increased in the antilymphocytic globulin treated group. Only one death from sepsis occurred in an extremely high risk recipient in the cyclosporin A group. When age was a risk factor, other risk factors were also frequently associated, such as severe cardiac disease, hypertension, obesity or malnutrition.

TABLE II

Effect of risk on patient survival in antilymphocytic globulin or cyclosporin A immunosuppressed patients

Risk Category	*Six Month Actuarial Patient Survival*				
	Group I (antilymphocytic globulin)		*Group II (cyclosporin A)*		*p**
	N	*%*	*N*	*%*	
Good risk	37	100	10	100	NS
High risk	27	88.5	7	100	$p<0.1$
Very high risk	15	78.1	9	100	$p<0.01$
Extremely high risk	21	71.0	4	75	NS

*Statistical comparison using Chi-square method.

DISCUSSION

Many authors have considered the effects of individual risk factors, present before transplantation, on the post-operative outcome. These determinants include age,[2, 13-16] preformed cytotoxic antibodies,[5] re-transplantation,[5] blood transfusion,[5, 6, 15] Fabry's disease,[17, 18] race,[7, 9, 15] malignant hypertension,[7]

glomerulonephritis,[7, 16] HLA-A, -B matching[14] and diabetes mellitus.[14] The preliminary analysis of risk factors in our transplant population has included these determinants as well as others in an effort to evaluate the cumulative effects of risk factors in renal transplantation.[10] This initial assessment categorised risk factors and assigned relative risk indices to each. When we applied this system to our transplant population, we found that, even though we did not employ a complex statistical analysis, our system was valid for grouping patients into risk categories as part of their pre-transplant evaluation. A relationship was observed between antilymphocytic globulin immunosuppressed patients in good, high, very high, or extremely high risk categories, and prognosis after transplantation.

It is apparent that a well developed system for determining the risk to life as part of the pre-transplant evaluation would be useful for decision-making both before and after transplantation. Accurate determinations of this risk could be used to individualise immunosuppressive therapy and would assist decisions regarding pursuit of re-transplantation after a graft has been lost to rejection. The results obtained from application of our risk categorisation system to cyclosporin A treated renal transplant recipients was affected by an overall reduction in patient mortality as compared with the previous antilymphocytic globulin treated group. Although our patient populations are small in both groups, this improvement in survival may be due to the steroid-sparing effect of cyclosporin A administration. Major risk factors such as cardiac disease and hypertension will cause fatal complications late in the course of the transplants, which will further influence survival.

We encourage other centres to utilise our system for risk categorisation or to modify it to accommodate the risk factors which may be additionally present in their patient population. In this way, risk categorisation may become an integral part of the pre-transplant patient evaluation and can be used to predict outcome after renal transplantation.

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Improved patient and graft survival using cyclosporin A in cadaver renal transplantation

R W G Johnson

SUMMARY

In two consecutive prospective randomised trials cyclosporin A has been compared with conventional immunosuppressive therapy (azathioprine and steroids) and with cyclosporin combined with steroids. The present report is a 4 year review and includes 165 patients.

Cyclosporin A alone had a significant advantage over conventional therapy at both 1 and 3 years ($p = 0.02$) for both patient and graft survival. No significant difference was seen when cyclosporin was combined with steroids. Nephrotoxicity was the most troublesome side-effect of cyclosporin A — but this resolved spontaneously on withdrawal of the drug.

INTRODUCTION

Since October 1980, 165 patients have been entered into two consecutive prospective randomised trials of the imunosuppressive drug cyclosporin A and have been followed up for a minimum of six months and a maximum of 4.5 years. In the first study cyclosporin A is compared with a conventional immunosuppressive régime of azathioprine and steroids. In the second, cyclosporin A alone is compared with cyclosporin A plus steroids. These studies have been conducted in a single centre with a large experience (600 patients) of conventional immunosuppressive therapy following cadaver renal transplantation.

PATIENTS AND METHODS

Only non-diabetic recipients of first and second cadaver renal grafts were considered. Every patient had previously received at least one blood transfusion; grafts were allocated on the basis of the least number of HLA-AB and DR mismatches. All patients received 500 mg methylprednisolone intravenously intra-operatively. Urine output was monitored hourly for the first six hours post-operatively and if it equalled or exceeded 50 ml/hr the recipient was entered into the trial by drawing a card to determine immunosuppressive therapy.

Group I Conventional therapy:
Azathioprine 3 mg/kg body weight
Soluble prednisolone 0.5 mg/kg body weight (to a maximum dose of 30 mg daily)

Group II Cyclosporin A alone:
Cyclosporin A was started as a continuous intravenous infusion 6 mg/kg body weight for 12 hr or until drugs could be accepted orally.

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Thereafter it was given in divided doses totalling 17 mg/kg/day in milk. The dose was reduced by 2 mg/kg at 2 weeks and 4 weeks, and then reduced monthly down to 5 mg/kg. In the event of toxic side-effects the dose was reduced by one-third. If toxicity continued or was intolerable the patients were switched to conventional therapy.

Group III Cyclosporin A plus steroids:

This group received cyclosporin A as above; in addition they were given low dose soluble prednisolone 0.25 mg/kg (to a maximum dose of 15 mg daily).

Acute rejection had to be distinguished from nephrotoxicity; this was most often accomplished by biopsy. Confirmed rejection was treated by daily injections of 1 g methylprednisolone for 3 days. It was a condition of the trial that only two rejection episodes should be treated in the cyclosporin A group and a maximum of 6 g steroid given. If graft function remained impaired or there was further deterioration the patients was switched to conventional therapy.

There were no serious imbalances of selection in any of the treatment groups. Age and sex were similarly distributed. HLA-AB and DR mismatches were close to 1.5 in the conventional group and 1.8 in the cyclosporin treated groups. All patients who lost their grafts and returned to dialysis were followed up for 1 year and included in the mortality data.

RESULTS

For ease of presentation and because the results were exactly the same the two cohorts of patients treated with cyclosporin alone have been combined.

Graft survival for the three treatment groups is shown in Table I. All patients who initially received cyclosporin are included in the graft survival analysis for the cyclosporin group, regardless of whether or not they were subsequently converted to conventional therapy ('intention to treat' principle). One year graft survival was 80.2% (65 of 81 grafts) in the cyclosporin alone group; this did not change significantly when steroids were added with survival at 78.6% (22 of 28 grafts). Both groups did significantly better than the conventional group where graft survival was 66% (37 of 56).

TABLE I

Graft survival

Group	*No.*	*3 months*	*1 year*	*2 years*	*3 years*
Azathioprine and steroids	56	78%	65%	57%	57%
Cyclosporin A alone	54	90%	80.2%	78.4%	78.4%
Cyclosporin A alone	27				
Cyclosporin A and steroids	28	95.2%	78.6%	74.9%	74.9%

Cyclosporin A alone and cyclosporin A with steroids are significantly better than azathioprine and steroids at every stage ($p = 0.02$).

Included in the cyclosporin alone group are 42 patients (51.8%) who were converted to conventional therapy (Table II) either because they required more than 6 g methylprednisolone for treatment of acute rejection (16 patients trial condition) or because of side-effects of cyclosporin (26 patients). One year graft survival in this sub-group is 76.2% (32 of 42 grafts): this is significantly better than for conventional treatment ($p = .02$). The incidence of conversion to conventional therapy was much lower (25% or 7 of 28), when steroids were combined with cyclosporin (Table III). This was because cyclosporin toxicity was reduced; conversion for rejection remained the same. Overall only one of 29 grafts was lost following conversion for toxicity whereas 13 out of 20 were lost when conversion was due to rejection.

TABLE II

Conversion from cyclosporin A to conventional therapy (No. at risk = 81)

Reason	*No.*	*Grafts lost*
Toxicity	26	1
Rejection	16	9 (56.25%)
	42 (51.8%)	10 (23.8%)

TABLE III

Effect of concomitant steroid therapy on rate of conversion from cyclosporin A to conventional therapy

Reason for conversion	*Cyclosporin A alone (No. at risk 27)*		*Cyclosporin A + steroids (No. at risk 28)*	
	No.	*Grafts lost*	*No.*	*Grafts lost*
Toxicity	11	0	4	1
Rejection	2	1	3	3
	13 (48%)	1	7 (25%)	4

In the cyclosporin alone group there were 3 deaths (Table IV), only one of which was related to immunosuppression. There were two deaths in the cyclosporin plus steroids group, one of which was due to viraemia. The highest mortality was in the conventional therapy group (6 of 56). Four of these could be attributed to immunosuppression.

The commonest side-effects amongst the cyclosporin treated patients were hirsutism 44%, fine tremor 39%, gingival hypertrophy 28%, nephrotoxicity 25%, hyperaesthesia 11% and hyperkalaemia 9%. Most of these side-effects were minor and all were dose-related. They disappeared rapidly when cyclosporin was withdrawn or its dose reduced sharply. Nephrotoxicity was the commonest reason for conversion to conventional therapy. In patients on conventional therapy the commonest side-effects related to steroid therapy: cushingoid

TABLE IV

Causes of death

Treatment group	*Diagnosis*	*Days post-op*	*Graft status*
Cyclosporin A alone	1. myocardial infarction	350 days	functioning
	2. cerebral thrombosis	115 days	functioning
	3. peritonitis (CAPD)	200 days	lost
Azathioprine + steroids	1. sepsis	170 days	lost
	2. cerebral thrombosis	41 days	functioning
	3. carcinoma pancreas	288 days	functioning
	4. viraemia (CMV)	43 days	lost
	5. viraemia (Herpes)	9 days	lost
	6. sepsis	130 days	lost
Cyclosporin A + steroids	1. viraemia	31 days	lost
	2. sclerosing peritonitis (CAPD)	252 days	functioning

appearance 54%, peptic ulceration 2% and diabetes 2%. These effects were also present when steroids were combined with cyclosporin. There was no difference in the frequency of bacterial, viral and fungal infections in the three groups but there was a difference in incidence of life-threatening infections. There were no life-threatening infections among the patients with cyclosporin alone whereas there were 8 in the conventional group resulting in 4 deaths and there were 3 amongst patients treated with cyclosporin and steroids resulting in one death.

DISCUSSION

These results confirm the view that renal allograft survival is greater in patients treated with cyclosporin alone as a first line immunosuppressive drug than in those treated with azathioprine and steroids. Our main interest in cyclosporin was its steroid-sparing potential; the significant improvement in graft survival without the side-effects of steroids was a bonus. The results we obtained for one year graft survival in patients treated with azathioprine and steroids accurately represent our previous experience with these drugs over the last 10 years. Improved graft survival (80.2%) with cyclosporin alone is similar to results obtained by the Cambridge group[1,2] and by the European Multicentre Study.[3]

Cyclosporin A differs greatly from all previously used immunosuppressive agents. The main problem in clinical use is distinguishing between nephrotoxicity and rejection. Most of the classical inflammatory features of acute rejection are absent. Serum creatinine is the only easily measurable determinant. Cyclosporin nephrotoxicity has been well documented[4,5] and it is known to disappear on withdrawal of the drug. In this study many people were treated for rejection and then converted to conventional therapy as a condition of the trial, only to discover in retrospect that nephrotoxicity had been the problem. This resulted in an unacceptably high rate of conversion, 51.8% to conventional therapy. Sixteen patients (20.15%) were converted for rejection and to avoid the consequences

of over-immunosuppression reported by the Cambridge group.[1] Of these, 10 subsequently lost their grafts. Twenty-five patients (30.8%) were converted for toxicity without graft loss. These changes reflect inexperience in the use of cyclosporin and also the lack of a meaningful assay. There is now evidence that much lower doses of cyclosporin can be used in conjunction with careful whole blood monitoring of the drug. Under these conditions improved graft survival is maintained and toxicity minimised. Our approach was to try and exclude rejection by biopsy and then reduce the dose by one-third. If a satisfactory result was obtained the dose was further reduced until the side-effects disappeared (therapeutic titration).

Graft survival results in the sub-group of patients converted to conventional therapy was 76.2%; this was still significantly better than the conventional group, and it is of particular interest that only one graft was lost when conversion was because of toxicity.

Steroids were combined with cyclosporin to see if graft survival could be further improved and in particular to see if nephrotoxicity was reduced. Graft survival was not significantly different when cyclosporin was given with maintenance steroids (78.6%) but the rate of conversion for toxicity was significantly reduced, 14.28% compared with 40.7%. Conversion for rejection was the same in the two groups. This advantage for maintenance steroids has to be balanced against the increased rate of steroid side-effects for no improvement in graft survival.

In these studies we have limited entry to recipients with primary renal failure which excluded diabetic subjects and only included grafts that exhibited prompt diuresis. This was done in order to minimise the variables. Clearly the steroid-sparing aspect of cyclosporin therapy should have advantages in the treatment of diabetics. Very few exclusions were made on grounds of no primary diuresis. 74% of kidneys used in this study were machine-perfused and, contrary to the Canadian Multicentre Trial Report,[6] this appears to have improved the rate of entry and in no way adversely affected the outcome. Cyclosporin A alone has now become our first choice immunosuppressive agent. We no longer convert for persistent rejection, preferring loss of the graft if necessary, and we are attempting to reduce toxicity by daily monitoring of whole blood trough levels of the drug.

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Twenty five years of haemodialysis. A tribute to the pioneer work of the Belfast Renal Unit

David N S Kerr

The first artificial kidney to be used in the British Isles was one of Kolff's original four which he donated to Hammersmith Hospital soon after the end of World War 2. It was used for a while in the late 1940's[1] but was then relegated to the basement when enthusiasm for the conservative treatment of acute renal failure was at its height. To my chagrin it is now displayed in a museum in the USA. Professor Darmady built a similar machine in 1946 and used it for a few years in Wessex.[2] However, haemodialysis only became a routine treatment for acute renal failure when Frank Parsons set up the Renal Unit in Leeds and imported an improved version of Kolff's rotating drum kidney. A similar machine was installed by Professor Shackman at Hammersmith Hospital a few months later and the RAF set up a unit at Halton under Sir Ralph Jackson. These three pioneer centres demonstrated to Britain what earlier trail-blazers like Swann and Merrill had shown America — that the artificial kidney was life saving in acute renal failure. From 1958 regional centres began to spring up all over Great Britain and Ireland starting with Dublin, Glasgow, Newcastle and Belfast.

The Belfast Unit was born in 1959, the year in which I made my own first acquaintance with the haemodialysis. I have described elsewhere[3] the sweat and tears, the hilarity and comradeship of those early years when the artificial kidney was a monster to tame, when its design was so crude that a manoeuvre as simple as inflating a cuff around a coil could almost double its efficiency[4] and when most of the equipment was improvised on DIY principles. Budding nephrologists were interviewed in their dungarees, spanner in hand, and they doubled up as nurse, technician, porter, engineer, dietitian and hospital cleaner. It was training on the job which left a permanent mark on Mollie McGeown and her generation.

A few months after the Belfast Unit was founded, an event took place which was to divert our attention from acute renal failure and reshape the history of renal medicine; regular haemodialysis for chronic renal failure started and has dominated the life of Belfast, and all other renal units, ever since.

THE BIRTH OF REGULAR HAEMODIALYSIS

In 1957 I met Dr Belding Scribner who had just arrived at Hammersmith Hospital for a sabbatical with Dr Malcolm Milne. It was no biblical sabbatical. He turned his inventive mind to writing teaching programmes in fluid and electrolyte balance; to devising bedside biochemical techniques 20 years ahead of the state of the art; to tinkering in the workshop with designs for indwelling cannulas; and to formulating the ideas which came to fruition on his return to Seattle. There,

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frustrated by his inability to keep an indwelling cannula patent, he had a chance conversation with a colleague who recommended the newly introduced material PTFE (Teflon). Two essential ingredients made the rest of the story possible. The first was his partnership with Wayne Quinton whose technical skill translated Scribner's ideas into practical hardware. The second was his unshakable faith that if he could overcome the technical difficulties he could prolong life in chronic renal failure by long-term haemodialysis. Scarcely another soul in the world shared his faith, but in 12 months he confounded his critics. In May 1985 the Royal Postgraduate Medical School paid its tribute to one of its most famous alumni by conferring on him the Fellowship of the School 25 years after the first successful treatment of chronic renal failure.

However, success was not instantaneous. In the early 1960's the trials of haemodialysis for acute renal failure were soon eclipsed by those of dialysis for chronic renal failure. Our faltering start in Newcastle was typical of the time. Excited by Scribner's first reports[5,6] we began to look on every young patient with chronic renal failure as a potential start to the Newcastle programme, but we had no suitable equipment, no space, no staff and no money to get started. One young man dying of renal failure, with a young wife and two small children to support, gave as his occupation "fruit machine operator". We wondered whether the night club owner who employed him could raise the cost of importing a Sweeden Freezer machine and Kiil dialyser from America. He was delighted to do so and set up charity concerts in all his night clubs, to which entertainers willingly gave their services free. In faith we ordered the machine and waited impatiently for the slow boat from Seattle. It arrived too late for our young man and we never saw a penny of the night club money. It was the only time we were let down, for from then on we forgot the rich and appealed to the poor. The ordinary folk of Northern England gave with unbelievable generosity, rivalled only by that of their opposite numbers in Ulster where Mrs Josie Kerr and her colleagues have done so much to support the Belfast Unit.

We were left with a big debt and an idle machine, but the latter was soon remedied. A Newcastle trained nurse with renal failure, who lived with her husband in Essex, was given a death sentence and came home to her parents for terminal care. We offered her the dubious privilege of being our first guinea pig and she jumped at it. Like most of the patients of that era she arrived almost in uraemic coma and went through three weeks of psychosis and confusion before pulling through to restored health. After 6 months she was transferred to the care of Dr Stanley Shaldon at the Royal Free Hospital and became Britain's first home dialysis patient. She died after 7 years of bravery in the face of innumerable challenges and vicissitudes, one of the many whose courage kept us going when at times the defects in our treatment seemed so great that it was scarcely worthwhile carrying on.

Today the patient of 35-54 years starting home haemodialysis has a better that 80% chance of surviving 5 years, and the young adult who receives a cadaver graft from haemodialysis or CAPD has a 90% chance of surviving 3 years.[7] This is still well below the life expectation of the rest of the population, but it is immensely better than the results recorded in the first two European Registry annual reports[8,9] when 40% of patients starting dialysis died in the first six months, 10% of deaths were due to cachexia, 10% of living patients had symptomatic peripheral neuropathy and the average patients received between 2 and 3 litres of blood per month. In this lecture I have tried to pick out the

advances in haemodialysis which I believe have contributed most to this transformation of the results in the last 2 decades.

ADVANCES IN HAEMODIALYSIS 1: ACCESS TO THE BLOOD STREAM.

The original Quinton-Scribner all-Teflon shunt was soon displaced by a much more convenient combination of a Teflon tip and a flexible silicon-elastomer (Silastic) tube. The original design had a U-bend under the skin to prevent the transmission of movement to the tip; this design is still in use at Hammersmith today, but in Newcastle we rapidly changed over to a straight tube which was much easier to declot with the help of a nylon tube. We did not routinely use the Ramirez winged modification, designed to improve subcutaneous stability, because it increased the difficulty of removing failed shunts. I am not aware of any controlled study comparing the longevity of these different designs but our clinical impression was that there was little to choose between them, so we chose the simplest and cheapest.

For a few patients the shunt was an ideal method of access. My longest lived leg shunt ran for 7 years with one revision of the venous tip and with the arterial site unchanged. For that patient, who did not engage in any rough work and was adept at bathing with one foot out of the water, it was hard to imagine a more convenient system. But for every one like that there were a dozen who suffered for their shunts and dragged down the average survival shown in Table I. This table is based on a survey carried out by a Newcastle medical student engaged in a student research project at the time when shunts were being replaced by fistulas. She recorded the life history of all shunts and fistulas carried out on the 100 or so patients then on dialysis in Newcastle. Since the majority of fistulas were still functioning and the majority of shunts had failed, a direct life-table analysis of the two methods was not very meaningful.

TABLE I

The fate of arteriovenous Silastic-Teflon shunts of patients surveyed in Newcastle-upon-Tyne, 1974

191 shunts inserted	
1 patient died with functioning shunt	
140 shunts failed	
45 shunts removed post-dialysis	
5 shunts still functioning	
Average life of site	11.4 months
Average gap between surgical revisions*	4.1 months

*Any procedure beyond simple declotting or thrombolysis.

However, Table I gives a sufficient glimpse of what the shunt did to the lives of dialysis patients. With a mean life for each shunt site of about 1 year and with an average of 3 reasonable sites on each upper limb and one on each lower limb, the threat of "running out of access" was real enough to give patients a constant source of anxiety even though, in practice, only one patient in Newcastle died primarily from this cause. Charting the remaining shunt sites, noting whether the arterial walls felt healthy and whether there were murmurs over the proximal

vessels, became part of the routine 6 monthly assessment of dialysis patients. However, the real problem with shunts was the effort required to keep them going. The commonest cause of failure was stenosis of the vein, less commonly of the artery, just proximal to the Teflon tip. At the site of the stenosis, thrombus formed readily, occluding the shunt. Patients were taught to monitor the shunt frequently, examining the colour of the blood in the Silastic tube, or listening over the vein with their stethoscope. Each time a shunt clotted they made a trip by car or ambulance, some of them travelling 100 miles or more to reach the renal unit; sat through an unpleasant declotting session and went home sometimes to find that the shunt had clotted again the same night.

Their great salvation was the Cimino-Brescia fistula. Table II shows the results obtained in 1974 in Newcastle. They were not the best in the world, but they were probably the sort of results that were obtained in most British units where one consultant and his rotating registrars shared the task of creating the fistulas.

TABLE II

(a) *The fate of arteriovenous (Cimino-Brescia) fistulas surveyed in Newcastle-upon-Tyne, December 1974*

191	fistulas inserted
35	(18%) failed within 48 hours
18	(9%) failed during subsequent dialysis experience
5	(2%) patients died with functioning fistula
70	(35%) received a transplant while fistula functioned
	13 of these failed post-transplant
	57 still functioning at time of survey
63	still functioning in dialysis patients

(b) *Effect of fistula site on early failure*

		Total	Failed by 48 hours	p
Radio-cephalic		139	23 (16%)	>0.05
All other sites		52	12 (23%)	
Anatomical snuffbox	13			
Antecubital fossa	19			
Saphenous loops	13			
Miscellaneous	7			

(c) *Causes of late fistula failure*

Thrombosis		8
Sudden, spontaneous	5	
Post-dialysis	2	
From compression	1	
Gradual stenosis		7
Infection and aneurysm		1
Ligation for heart failure		1
Haemorrhage at each dialysis		1
		18

For most patients the radial fistula was the single answer to blood access; it lasted them until their successful transplant and often remained patent to await their return to dialysis if the transplant failed. The radial fistula's long life expectation and relative freedom from complications gives it a long lead over the many alternatives which are rightly used as secondary measures when the fistula fails or cannot be created: proximal fistulas, saphenous loops or straight grafts; expanded PTFE (Gortex) grafts; bovine heterografts; Thomas appliqué shunts etc. These second and third line measures are required because patients live longer. In 1979 the EDTA-ERA Registry had records of more than 3000 European patients who had survived more than 10 years on renal replacement therapy; about a third had never been transplanted.[10] Today there must be several thousand patients in their second decade of haemodialysis; one centre has a 15 year survival of 65%.[11] However, the relatively short survival and the complication rate of all alternatives to the radial fistula justify Dr Lumley's description of vascular access as the Achilles heel of haemodialysis, even in 1984.[12] The difference is that it is now the Achilles heel for a few patients when, in the era of the shunt, nearly every patient fervently wished he had been completely immersed in the Styx.

I therefore view as the most hopeful recent development in blood access the increased attention to preserving the radial fistula. Immediate exploration of fistulas that fail early can often save one fistula site. Late failure can be anticipated, the fistula studied by ultrasound or digital subtraction angiography and stenosis treated by balloon angioplasty or surgical revision. However, I believe that the biggest contribution in Britain could come from more use of skilled surgeons for the initial fistula operation. This is not a job for the casual surgeon. Most nephrologists take the view that registrars should not learn to do renal biopsies unless they plan to become nephrologists, when they should be thoroughly trained. If the same approach were adopted in vascular access surgery, many of our problems would fade away.

However, there are a few patients whose tiny veins after prolonged steroid therapy and careless misuse during their earlier treatment would challenge any surgical virtuosity. Chronic staphylococcal carriers are at risk whatever blood access is used; one of ours lost 12 blood and peritoneal access sites and one transplant from infection; for such patients prolonged indwelling tubes in the subclavian vein or vena cava have proved life saving, even though their liability to septicaemia persists.[13]

ADVANCES IN HAEMODIALYSIS 2: SINGLE NEEDLE DIALYSIS.

In the era of the shunt, the dialysis circuit was designed to pump blood out of the arterial end and back into the venous end. When the fistula was introduced, the circuit was simply attached to two needles, a distal (arterial) one and a proximal (venous) one. Several years passed and thousands of fistulas were punctured hundreds of times before it occurred to anyone that it would be kinder to the patient and easier for the staff if we inserted one needle rather than two.[14] Kopp's original solution to this problem was to occlude the venous and arterial line alternately by means of a lever which flicked rapidly across from one to the other. A single blood pump pushed blood into an expanding dialyser for a few seconds then sucked on an empty line for the next few seconds while the dialyser drained into the patient. There were two big disadvantages to this system. Modern dialysers, particularly hollow fibre dialysers, have a low compliance so the system

had to switch back and forth too frequently for efficiency. Some recirculation inevitably occurred at each switch. This problem was overcome very simply by inserting an expansion chamber into the arterial line. The second problem was harder to overcome; to achieve a high blood flow through the dialyser, the drainage phase had to be fast and therefore the pressure in the dialyser had to be kept high. This produced a high obligatory ultrafiltration. The proportionating machines of the 1970's did not have controlled transmembrane pressure, so the ultrafiltration had to be compensated by saline infusion and the risk of hypotension was considerable.

The second problem was elegantly circumvented by the use of a twin-head pump which accelerated the drainage phase and gave the operator complete control over the pressure in the blood compartment; indeed this system permitted the use of high flux dialysers in open circuit for the first time.[15] Despite the intermittent flow through the dialyser, its efficiency at a given flow rate per minute was the same as that with a conventional two needle, continuous flow arrangement.[16] Unipuncture proved so popular with patients in Ghent and Newcastle that it was adopted as the standard practice in both centres. However, the extra cost of the twin-head pump has deterred others from using it, and it remains the minority treatment worldwide. The last development has been the marketing of double lumen needles which give a higher flow through the dialyser, and therefore a better dialysis efficiency than tidal flow,[17] provided the fistula is of sufficient size. Double lumen subclavian catheters bring the same advantages to temporary access but with a greater need to watch for recirculation, by checking the plasma urea in the arterial and venous lines and in a vein of another limb, if there is any suspicion that dialysis efficiency is inadequate. (Kerr's rule-of-thumb is that the post-dialysis plasma creatinine should be half the pre-dialysis or less).

Single needle dialysis is underused. It has been widely adopted in acute renal failure, where it is a godsend to patients with multiple demands on their veins. It had been neglected in the treatment of chronic renal failure, where it is not usually life-saving but is an added measure of comfort, convenience and reassurance to many patients. The reluctance of dialysis staff to change their routine, and take the little extra trouble is, I believe, a bigger constraint on its use than cost. Perhaps this is a sign that doctors on dialysis units spend less time listening to the lesser complaints of their patients than they did when Kopp invented unipuncture.

ADVANCES IN HAEMODIALYSIS 3: PROPORTIONING.

When regular haemodialysis began, we all used recirculating baths. They were cheap, effective and easy to maintain; these qualities have kept them in use in many countries for a decade after they disappeared in the British Isles. However, they had several disadvantages of which the worst was the difficulty of sterilising them between dialyses. Bacterial build-up was a constant threat, and I have seen patients looking slightly seedy as they finished their dialysis against a bath of what looked like pond water and contained $>10^5$ *alkaligenes faecalis* or some other nasty organism per ml.

The first proportioning machine was designed by Babb and his colleagues at Seattle.[18] It was unveiled at a conference in December 1964 which marked the birth of home haemodialysis. It was not really essential to dialysis in the home, which has been conducted successfully with recirculating systems, but it reduced the drudgery and it stimulated manufacturers to improve the monitoring. The drudgery of home haemodialysis is dismissed too airily by enthusiasts for this

form of treatment. At that inaugural conference the world's first home dialysis couple were interviewed on television and asked how they spent their evenings. "Mondays, Wednesdays and Fridays, we dialyse" they replied. "Tuesdays, Thursdays and Saturdays we clean up and get ready". "And Sundays?" asked the interviewer. "We flop!". The steady, and very impressive, improvement in the design of proportioning machines, which has largely been the work of industry, has made life for the home patient more tolerable than it was in 1964, though it is still a heavy burden to impose on any family.

ADVANCES IN HAEMODIALYSIS 4: MONITORING.

Monitoring was developed in parallel with proportioning and has not changed fundamentally since the 1960's. The choice of parameters that required constant observation — dialysate pressure, temperature, conductivity and flow rate, venous bubble trap pressure and suction on the arterial line — have proved wise choices. There were three other measurements that clinicians wanted from the start but which proved much harder to provide: ultrafiltration rate, blood flow rate and presence of air or froth in the venous blood line.

The first machine to give a reliable measure of *ultrafiltration* was the Rhodial,[19] designed to curtail ultrafiltration from the high flux RP6 dialyser. It had a closed dialysate compartment from which the ultrafiltrate was displaced into a measuring cylinder. A miniaturised version of this system has been adopted in other machines designed for single-pass dialysis; the dialysate compartment adjacent to the dialyser can be sealed off for a few seconds during which the ultrafiltrate is measured in a small flow meter.

Several ingenious devices for continuous measurement of ultrafiltration have been built and a few marketed; they have depended on comparing the inflow to and outflow from the dialyser, which differ by about 0.2–2.0% depending on the ultrafiltration rate. The very precise measurement of flow rate demanded by this exercise has so far defeated the instrument makers. Consequently some machines calculate ultrafiltration rate from the transmembrane pressure, which is computed from pressure measurements at inflow and outflow of both compartments of the dialyser. The final solution of this problem remains a challenge to the designers.

Accurate measurement of *blood flow rate* is required for research purposes but not for clinical dialysis. Pump speed gives a reasonable measure of blood flow if there is a monitor to detect excessive suction on the arterial line, and bubble transit time over a measured track is an acceptable check. Consequently no manufacturer has made the necessary investment to provide us with a Doppler or similar blood flow meter which is robust and reliable enough for clinic use — a pity because it would be a help in patient care.

Detecting *air in the venous line,* on the other hand is a matter of life and death. However, many British clinicians were slow to adopt air-embolism monitors because they rightly believed that the best way to prevent air embolism was to prevent air entering the circuit, by having all infusion points down stream of the pump. The early monitors, which relied on the creation of an uninterrupted light path in the bubble trap or venous line, were easily fooled by froth. However, it is difficult to eliminate some causes of air embolism such as splits in the blood pump inserts[20] or displacement of the arterial needle during sleep, so it would be difficult to justify the omission of an air embolism monitor now that the capacitance and

ultrasonic detectors have reached a high degree of reliability.[21] They certainly add greatly to the confidence of home dialysis patients. Even remote risks become important when home dialysis patients survive beyond 10 years and perform 2000 or more dialyses in the home.

ADVANCES IN HAEMODIALYSIS 5: DE-AERATION.

Cold water contains more dissolved air than warm water. When cold mains water is rapidly heated in a proportioning unit the dialysis fluid becomes supersaturated with dissolved air. The surplus oxygen and nitrogen diffuse through the membrane into the blood which forms bubbles as the pressure is reduced during its passage through the dialyser and into the venous bubble trap. The problem is encountered almost exclusively among home dialysis patients during winter in Northern regions; we saw a lot of it in Newcastle. Some of our home dialysis patients had to wake themselves by alarm clock hourly during the night to empty the bubble trap of froth and prevent air embolism.

The first partly effective de-aerators heated the incoming water rapidly to release air, then cooled it in a heat exchanger. Water temperature rose by about 10°C which caused no problems in Britain but was a challenge to ingenuity in the tropics. One resourceful Singaporean wife solved the problem by filling the domestic bath with "cold" water overnight, then pumping this de-aerated water into her husband's proportioning machine, by-passing the heater and heat-exchanger. Such labours are now unnecessary, for the problem was eliminated by the use of efficient suction de-aerators.[22]

Demonstrating the cause of this problem and persuading manufacturers to take it seriously and overcome it by better design was one of our most satisfying adventures in dialysis. It has now gone from the dialysis unit into the history books.

ADVANCES IN HAEMODIALYSIS 6: ULTRAFILTRATION.

A more important advance was announced by Jonas Bergström at the Hamburg Congress of EDTA in 1976. He described his simple chance observation that ultrafiltration through a dialyser with the dialysate pathway unconnected allowed rapid removal of fluid without the haemodynamic disturbances seen during haemodialysis.[23] The Chairman, Dr Stanley Shaldon, congratulated him on " . . . the most important paper I have heard in the dialysis field in the last decade". It was no exaggeration. Bergström's observation has been abundantly confirmed and widely applied in the emergency treatment of fluid overload in both acute and chronic renal failure.

Bergström went on to develop the technique of sequential ultrafiltration-haemodialysis which sought to avoid dialysis hypotension by separating fluid removal from solute removal. There is much anecdotal support for this widely used method, but our own controlled trial failed to show any advantage over conventional haemodialysis.[24] It could be criticised because the patients were unselected, not chosen because of their liability to dialysis hypotension, but I am unaware of any subsequent trial that has overturned the verdict.

Whatever the eventual place of sequential ultrafiltration it brought us one great advance. Its use led manufacturers to develop proportioning machines with controlled transmembrane pressure so that the doctor, nurse or home patient can control ultrafiltration at will.

ADVANCES IN HAEMODIALYSIS 7: DIALYSER DESIGN.

One of the nightmares of the 1960's was building the Kiil dialyser and then waiting on tenterhooks for the air-pressure test that so often signalled a membrane leak and the need to start again from scratch. At the inaugural conference on home dialysis a doctor who was himself a dialysis patient looked at the first proportioning machine with all its monitoring and exclaimed "Don't make me feel like spaceman, just design a dialyser that does not leak". Long after the first man walked on the moon we had coil dialysers with a 10% leak rate. Today a leak rate of 0.1% is not exceptional and we owe a great debt to Werner Bandel and his successor at ENKA AG who perfected the manufacture of Cuprophan and first gave us leak-free membranes.

One of my privileges since 1970 has been to work with the manufacturers of dialysers, test their products, advise them on design improvements and report the findings to the Department of Health and Social Security who distributed them to renal units. The architect, and often the artisan, of our studies was Dr N A Hoenich whose work has recently been summarised in a DHSS Bulletin.[25]

There was a period of excitement and intense activity in the early 1970's reminiscent of the early 1900's in motor car design or the last decade in computer technology. Small companies sprang up and bright ideas tumbled off the drawing boards in rapid succession. Untroubled by the entanglement of regulation which now emeshes the designer, they experimented freely with new materials and in 3 short years doubled the performance of the artificial kidney. DIY doctors joined in the fun; the most important advance in membrane supports was the work of Dr Holtzenbein who spotted an interesting plastic mesh in the upholstery of his Volkswagen. The pace of advance has slowed, but the need for it has also diminished. Today's dialysers are compact, convenient, reliable and efficient; their cost (corrected for inflation) is about one-twentieth that of the first disposable dialyser.

ADVANCES IN HAEMODIALYSIS 8: WATER TREATMENT.

The British renal failure services started on a shoestring and has swung on it ever since. One disastrous result was the conscious decision that, when treatment was limited by funds, we could not spend part of our limited budget on the cost of full water treatment. By 1973 I had come to doubt the wisdom of this policy, and at a meeting on water for dialysis[26] I admitted that we had no proof that water treatment prevented any of the complications of dialysis, but said that I visualised myself one day standing in a court of law and conducting a conversation with the prosecuting counsel which ran like this:

Counsel: My client claims she has bone rot (and) brain rot . . . because you are making her dialysis fluid with impure water.

DNSK: We use only the best tap water supplied by the Newcastle and Gateshead Water Company and passed fit for human consumption.

Counsel: My client says you give her 300 times as much water through her dialyser as the average citizen drinks . . . .

DNSK: Our tap water is not known to contain anything that causes bone rot and brain rot . . . .

Counsel: Does it contain no identified impurities?

DNSK: It contains some . . . (I listed the many sources of impurities in tap water from the Cheviot Hills to the taps and finished . . .) . . . we put flocculating agents into our water to get rid of the colour, chlorine to get rid of the bacteria, fluoride to help the bairns' teeth . . . .

Counsel: No doubt you monitor all these impurities regularly . . . ?

DNSK: No, but we get an annual report from the Water Company . . . .

Counsel: Are you sure that none of the substances you study in so cavalier a manner are harmful?

DNSK: No, but we are studying them . . . .

Counsel: When do you hope to complete these studies?

DNSK: Maybe in 50 years' time.

Counsel: By that time the answers will have ceased to interest my client.

I concluded "Because of this sort of consideration, rather than because the case is proven, I suspect that all of us will eventually decide to err on the side of safety (and expense) by removing all contaminants and forgetting about them".

My suspicion proved unfounded. My own Health Authority was unconvinced by the argument; we continued to use water softeners as our main method of water purification and in Newcastle alone 27 patients suffered the brain rot to which I alluded and 23 died; about 200 suffered disabling illness from the bone rot, now known as aluminium osteodystrophy. The story was repeated all over Northern and Western Britain. Like the road users who are protected from an accident black spot only when enough people have died at it, our patients received the protection of adequately purified water only after an unacceptable sacrifice that could have been forseen and indeed was foreseen and predicted.

Now the threat of encephalopathy and disabling bone disease has been removed and as a by-product the other, less important identified impurities like fluoride, chloramines and lead can be forgotten.

ADVANCES IN HAEMODIALYSIS 9: FREEDOM FROM FEAR.

Many fears haunted the pioneering patients in this form of treatment, not least the fear of death. Some of these fears have been largely removed.

Hepatitis B was a real menace to patients and staff in the 1960's and 1970's. It was largely eliminated from British units by rather draconian hygienic measures, isolation of carriers and, in a few cases, refusal to accept hepatitis carriers for dialysis. The fear of hepatitis reached ludicrous lengths. I remember sacks of perfectly functioning or readily reparable telephones on their way to the incinerator because they had been in the home of a dialysis patient, often one who was more certainly free of hepatitis than the telephone engineer who removed them. Specific immune globulin and vaccination against Hepatitis B have removed much of the fear and given our patients once again the freedom to travel abroad on holiday, though sadly the shadow of AIDS now hangs over that newly-found freedom. I welcome the chance to say "Thank you" to the many kind donors who provided holiday homes around Britain and to Mrs Elizabeth Ward who had the imagination to provide hepatitis-free holiday centres in Britain and abroad through the BKPA, for giving our patients the chance of a much-needed break in the days when fear of hepatitis kept them at home.

Dialysis itself was once greeted with foreboding. In the 1960's it was common to see most of the patients in a dialysis session vomiting into their kidney dishes. Cramps were a common and miserable accompaniment of dialysis. Headache during the procedure and lassitude after it were almost universal. We have learned a lot about the causes of these complications but not enough to explain the dramatic fall in their incidence. With no proof to back it up, it is my strong hunch that many of the symptoms were caused by contaminants in dialysis fluid, dialysers, circuits etc which have been eliminated by better equipment and techniques without our ever identifying them. Copper, zinc and nickel from metal parts in contact with feed water or dialysate, plasticizers from tubing and silicone particles from blood pump tubing have all been identified as causes of acute or chronic symptoms, and it is anyone's guess how many more transient contaminants have done their harm and disappeared undetected.

Pyrogen reactions were a particularly nasty complication of dialysis. They usually started within the first hour of dialysis, caused angor animi, chest pain, rigors and general misery which slowly subsided over the few hours after the temperature peaked. Crops of facial herpes were a nearly universal sequel. In the literature of the 1960's and 1970's they were nearly always blamed on bacteria or pyrogens contaminating the dialysis fluid, although their timing and epidemiology were seldom in favour of this theory and several authors failed to demonstrate passage of pyrogens across dialysis membranes. Pyrogen reactions complicated 30% of dialyses in our first year at Newcastle, when we used non-disposable blood circuits and several subsequent outbreaks were traced to contaminants in the blood pathway. I believe that the virtual disappearance of this frightening complication of dialysis is due to the use of disposable dialysers which are now manufactured with stringent precautions against contamination with pyrogen. Whatever the reason, patients no longer have to endure or fear them.

ADVANCES IN HAEMODIALYSIS 10: ESCAPE TO ALTERNATIVES.

CAPD has arrived to give the haemodialysis patient an alternative if it suits his life-style better or if his vascular access sites are used up. However, the biggest single change in his lot is the greater chance of successful renal transplant. It is here that Belfast has made its greatest, and all-important, contribution. By maintaining a high success rate throughout, by reducing morbidity with the low-steroid regime and by providing almost enough transplants to provide for the needs of its Region, Belfast has inspired the rest of the UK during the years when we trailed behind.

ADVANCES IN HAEMODIALYSIS 11: BETTER MEDICAL UNDERSTANDING AND CARE (The Belfast factor).

In this talk I have concentrated on the technical advances which have had immediate and visual impact on the results of regular haemodialysis. Of equal importance has been a growing medical knowledge of what is involved in "life after renal failure". That knowledge now generates a new edition of Drukker, Parsons and Maher[27] every 3 or 4 years, its 49 chapters bearing an average of about 200 references to original articles. It is to this corpus of medical knowledge, rather than to the technical details, that the Belfast team has made its many contributions. With a fine blend of scientific curiosity and concern for patients they have looked at practical problems like gastrointestinal bleeding, seeking its cause in the pathophysiology of the hormones governing gastric secretion[28] and applying that knowledge to the prevention of the disease.[29]

Above all, however, we acknowledge that *the* Belfast contribution is the maintenance of the highest clinical standards in medical care. That is the only explanation that has been found for the outstanding success of the Belfast transplant programme, and it also accounts for the success of their dialysis programme.

ENVOI

On the 25th anniversary of the foundation of the Belfast Renal Unit, I say to Mollie McGeown and her fellow pioneers: "It has been a wonderful quarter century to live through; we have seen the transformation of this form of treatment, and it owes a lot to your example. It has been fun and inspiration to share these years with you and I hope your next 25 years, and ours, will be just as rewarding".

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