Morbidity and mortality of long-term haemodialysis: a review[1]

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Haemodialysis has been available for more than 20 years. The current annual cost of hospital dialysis is approximately £12 000 per patient. There were 3577 haemodialysis patients in Britain in December 1981 (Wing *et al.* 1983). Retting (1980) has estimated that by 1995 in America the cost of renal replacement therapy will reach $4.6 billion each year if current practices are unchanged. Figures for long-term survival are now available and it is therefore possible to discuss morbidity and mortality. Haemodialysis is very safe: the risk of death due to technical or human error has been estimated as being only one in 76 138. Over ten years the chance of a dialysis-related death is quoted as 2% (Friedman & Lundin 1982).

Long-term survival on haemodialysis

Table 1 summarizes the findings of six series. The figures of Jacobs *et al.* (1981) represent average success because they are compiled from 32 European and adjacent countries involving about 1000 dialysis units. Thus results from excellent units are balanced by the less successful, giving an approximate measure of success.

There is a gloomy catalogue of complications which may befall a haemodialysis patient.

Cardiovascular complications

Persistent hypertension is the major risk factor for cardiovascular deaths since hypertension is a primary independent risk factor for coronary heart disease, heart failure and arrhythmias. Hypertension is almost invariable in terminal renal failure and does not respond in a substantial minority of patients during dialysis. In a few patients bilateral nephrectomy is required (Wilkinson *et al.* 1970). This usually achieves normal blood pressure but the procedure has an appreciable morbidity and mortality. Charra *et al.* (1983) dialysed their patients for 24–30 hours weekly, restricted salt intake, instructed their patients to gain no more than 2.5 kg between dialyses, needed to use no hypotensive drugs and observed no cerebro- or cardiovascular deaths over a ten-year period of observation. Contemporary high-performance dialysers are capable of achieving satisfactory biochemical and fluid control when used for 10–12 hours weekly. Degoulet *et al.* (1982) reported a 44% cardiovascular death rate over six years. Two risk factors were elevated systolic and diastolic pressures. Neff *et al.* (1983) found a relationship between hypertension and cardiovascular death.

The hypertriglyceridaemia of chronic renal failure (Bagdade *et al.* 1968) does not remit with the inception of dialysis (Ibels *et al.* 1975). As a consequence of hypertriglyceridaemia, serum cholesterol concentrations are normal or low normal and there is a reduction in high-density lipoprotein cholesterol concentrations (Daubresse *et al.* 1976). These abnormalities are considered to be consequent upon reduced activity of lipoprotein lipase in uraemic patients (Coplon *et al.* 1983). This analysis has been challenged (Rostand *et al.* 1979, Charra *et al.* 1983, Burke *et al.* 1978). Current opinion (Kettner & Ritz 1982) regards hypertension as the major risk factor for vascular disease.

Few authors have analysed the effects of cigarette smoking upon cardiovascular mortality. Haire *et al.* (1978) showed that half a group of dialysis patients who smoked died within five years of starting treatment while 78% of non-smokers survived ten years.

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Table 1. Long-term survival and fatal events in six large series of chronic haemodialysis patients. All age groups are pooled

Reference	No. of patients	Length of observation (years)	% survival	Percentage death rate due to				
				Cardiovascular disease	Infection	Malignancy	Suicide or withdrawal	Other or unspecified
Jacobs *et al.* 1981	4536●	>10	25	—	—	—	—	—
Degoulet *et al.* 1982	1453●	6	85	43.9	13.1	5.6	2.0	23.7
Neff *et al.* 1983	83	10	18	18.7	15.7	1.9	1.9	9.4
Vollmer *et al.* 1983	594	12	25	—	—	—	—	—
Charra *et al.* 1983	52	10	85	0	5.7	0	0	0.5
Laurent *et al.* 1983	373■	10	75	32.5	14.9	7.1	12.3	52.6
		15	65	48.7	22.4	10.6	18.5	78.9

A dash indicates absence of data
● multi-centre series
■ patients reviewed at 10 and 15 years

The cardiovascular system in chronic dialysis patients is subject to a number of other stresses: hypotension may occur during dialysis; volume overload may occur between dialyses; the concentration of plasma solutes may change rapidly whilst dialysing, perhaps engendering cardiac arrhythmias. The most common arrhythmia is premature ventricular beats (Blumberg *et al.* 1983); only rarely was an R on T observed. Whether arrhythmias (other than those related to hyperkalaemia) contributed to cardiovascular deaths in dialysis patients has not been determined (Lakier & Levin 1981).

Infection

Table 1 indicates that infection is an important cause of death. Whether dialysis patients are more prone to bacterial infection than others is debated; adequate controls are unavailable. The usual pathogens occur, with a greater chance of staphylococcal septicaemia. This is related to skin bacteria gaining access to the circulation during needling of the arteriovenous fistula prior to dialysis. Humoral (Giacchino *et al.* 1982) and cellular (Raska *et al.* 1983) immunity is impaired in chronic uraemia. These deficiencies may be enhanced by malnutrition (Mattern *et al.* 1982). They do not improve with prolonged dialysis. Conversely, symptoms related to viral-like illnesses may well improve during dialysis: presumably products of inflammation are removed by, or bound to, the membranes of the dialyser. This has not been systematically investigated.

There is a 10 to 15-fold increase in the incidence of tuberculosis (Lundin *et al.* 1979, Andrew *et al.* 1980). The nonspecific symptoms of tuberculosis in those already unwell tend to delay diagnosis. The mortality rate has been reported to be as high as 38% (Mattern *et al.* 1982).

Malignancy

There is debate whether chronic uraemia predisposes to the development of cancers (Kjellstrand 1979). Many varieties of tumour have been recorded in uraemic patients, the incidence in one series (Lindner *et al.* 1981) being as high as 9.5%. Only two groups could not demonstrate an increased risk of tumour development (Slifken *et al.* 1977, Bush & Gabriel 1984). There is an increased incidence of non-Hodgkin's lymphoma in dialysis patients (Kinlen *et al.* 1980, Wing *et al.* 1983, Kantor *et al.* 1983). All studies lack adequate controls for the very highly selected patients. A comparison of the incidence of malignancy between a group of dialysed and non-dialysed uraemic patients is needed, since haemodialysis may introduce an additional risk.

Suicide or withdrawal from dialysis

Chronic haemodialysis does not allow the return of normal health. Many medically minor but psychologically important events reduce the quality of life (Gabriel 1982). Dialysis itself may be stressful or unpleasant, restrictions in social and occupational activity may be unacceptable, loss of income is worrying, dependence upon a machine to maintain life is repugnant to some, dietary and fluid discipline is beyond others, sexual failure and marital disharmony are not uncommon, whilst anxiety regarding vascular access, transplantation and longevity occupy many. It is not surprising that there is substantial psychiatric morbidity (Kalman *et al.* 1983, Zetin & Deitch 1983). Dialysis patients are taught those foods which are high in potassium. Some ignore this advice or use the information for suicide if the toll of dialysis becomes too high. Others take conventional overdoses of drugs. A few patients purposely withdraw from dialysis programmes. Suicide or withdrawal caused the death of 68 patients out of 373 over a 15-year period in the series reported by Laurent *et al.* (1983) (Table 1).

Accidental hyperkalaemia is probably underestimated. Degoulet *et al.* (1982) and Neff *et al.* (1983) indicated that 5.1 and 2.5% of their patients respectively died of hyperkalaemia. Neither hyperkalaemia nor ventricular fibrillation due to myocardial ischaemia is detectable at post-mortem.

Systemic disease and dialysis

The three-year survival rate for diabetics treated by hospital haemodialysis between 1979 and 1982 was 50% for those aged 15 to 34 years, and 23% for those aged 65 and over. Comparable figures for non-diabetics are 84% and 47% respectively (Wing *et al.* 1983).

By contrast, systemic lupus erythematosus (SLE) almost invariably remits when advanced azotaemia develops and immunological variables return to normal (Mordasini *et al.* 1977). Jarrett *et al.* (1983) found that in a group of 14 patients with SLE receiving haemodialysis five-year survival was 58.6% compared with 88.5% for 62 non-SLE renal failure dialysis patients. Disease activity was minimal and primarily involved brain and synovium.

Amyloid renal failure has been considered a contraindication to haemodialysis. Generally the patient with amyloid fares worse on dialysis than others, especially if nephrotic or hypoalbuminaemic when treatment starts (Avram *et al.* 1976). The two-year dialysis survival rate is 52% compared with 76% for all other patients on the European Dialysis and Transplant Association Registry (Gurland *et al.* 1976). Familial Mediterranean fever may be ameliorated by haemodialysis (Rubinger *et al.* 1979).

Patients with terminal renal failure due to progressive systemic sclerosis tend to fare poorly when dialysed (Le Roy & Fleischmann 1978, Simon *et al.* 1979, Traub *et al.* 1983).

The future on dialysis for patients with polyarteritis nodosa and Wegner's disease (Kuross *et al.* 1981, Pinching *et al.* 1983) appears less gloomy than for those with scleroderma, although with these rare conditions experience is limited.

Renal osteodystrophy

Secondary hyperparathyroidism, osteomalacia, osteoporosis, fracturing osteomalacia and growth stunting are secondary to altered calcium and phosphate metabolism.

In chronic renal failure the kidney is unable to respond to parathyroid hormone (PTH) and consequently the skeleton bears the brunt of chronically-raised concentrations of PTH (Coburn *et al.* 1969). Bone disease is histologically present in 90% of patients at commencement of dialysis (Ellis & Peart 1973). Osteitis fibrosa is more common in Australia than in America, while the reverse is true for osteomalacia (Ihle *et al.* 1982). Geographical variations of renal osteodystrophy are well recognized in Britain.

Symptomatic bone disease tends to increase in frequency and severity in proportion to duration of dialysis. There is debate as to whether treatment of dialysis osteomalacia with synthetic analogues of vitamin D is beneficial (Kerr 1981). Osteitis fibrosa may be prevented by treatment with synthetic analogues before symptoms develop (Memmos *et al.* 1981) or respond well to treatment (Voigts *et al.* 1983). For symptomatic patients, subtotal

parathyroidectomy (Stanbury *et al.* 1960) is a very successful procedure, symptoms often ceasing within 48–72 hours. Postoperatively serum calcium concentrations fall sharply within hours (Dawborn *et al.* 1983) and the reciprocal hyperkalaemia may be fatal.

Much of the literature on renal osteodystrophy before the late 1970s is now suspect because of the importance of aluminium in the genesis of a form of osteodystrophy previously unrecognized (Kerr 1981). A patient is dialysed against 360 to 420 litres of water weekly or even more if prolonged dialysis is used (Charra *et al.* 1983). Impurities in tap water may be dialysed into the patient. Aluminium transfers from dialysate to patient if the dialysate has a high aluminium concentration (Kaehny *et al.* 1977). Fracturing renal osteodystrophy is a progressive form of osteomalacia which begins two to four years after starting haemodialysis; bone pain, myopathy and spontaneous fractures occur. There is clear evidence that high dialysate concentrations of aluminium from unmodified tap water enhance development of this osteodystrophy (Wills & Savory 1983). Analogues of vitamin D are unhelpful (Voigts *et al.* 1983). Waterborne aluminium can be substantially reduced by de-ionization or reverse osmosis (Ward *et al.* 1978, Davison *et al.* 1982, Wills & Savory 1983). Desferroxamine may be of value in chelating and removing aluminium from patients (Ackrill *et al.* 1979).

Osteomalacia, osteitis fibrosa and osteoporosis frequently coexist (Evans *et al.* 1982). Osteomalacia usually predominates. Bone mineral content diminishes with increasing years of dialysis (Rickers *et al.* 1983) but is slower if the calcium × phosphate product is normal.

Brain dysfunction

Maintenance dialysis patients are subject to many neurological disorders – dementia, drug toxicity, air embolism or haemorrhage related to anticoagulants. Gilli *et al.* (1980) reported progressive moderate decline in intellect and memory in 8 patients aged 30–58 years studied after four years of therapy, which correlated with concentrations of serum aluminium and PTH. Conversely, Brancaccio *et al.* (1981) were unable to demonstrate any change in higher cerebral function in a group of 10 similar patients. Dialysis dementia is due to deposition of aluminium in the brain. It is characterized by abnormalities of speech, myoclonic jerks, personality changes, convulsions and finally global dementia leading to death in adults (Sideman & Manor 1982) and children (Rotundo *et al.* 1982). The condition is preventable (Wills & Savory 1983) and should cease to occur (Sideman & Manor 1982).

Liver disease

Infection by hepatitis B virus (HBV) was once a distinct risk in British units. However, since the application of the principles set out in the Rosenheim Report (1972) it has become rare in Britain for a patient to develop HBV hepatitis or the carrier state. No other country has imposed such strict rules; consequently HBV infections are not uncommon elsewhere. For this reason dialysis patients have been discouraged from taking holidays abroad where they would risk HBV infection. The introduction of a vaccine against HBsAg (Desmyter *et al.* 1983) appears to be very effective in patients and staff. Hepatitis A, non-A non-B hepatitis and hepatides caused by cytomegalovirus and herpes simplex virus occasionally occur, but are more common after transplantation (Sopko & Anuras 1978). Hepatic dysfunction, as yet of unknown importance, has been described following iron overload (Gokal *et al.* 1979, Ware *et al.* 1979) and by migration of particles of silicone from blood-pump tubing (Leong *et al.* 1982).

Access surgery

The subcutaneous lower arm fistula (Brescia *et al.* 1966) rapidly gained popularity. It is not invariably successful. Inadequate blood flow or thrombosis necessitate readmission for surgery to re-establish adequate vascular access for haemodialysis.

Transplantation of the saphenous vein from thigh to forearm usually provides an adequate conduit for a fistula. If suitable vein for transplantation is unavailable, the use of a polytetrafluoroethylene graft provides satisfactory access, but only 50% of such grafts are

patent at 18 months (Tordoir *et al.* 1983). The development of subclavian catheters for short-term access to the circulation has been valuable. Apart from the introduction of infection, malposition of such cannulae has necessitated emergency cardiothoracic surgery which in some has proved fatal (Barton *et al.* 1983).

Carpal tunnel syndrome

There have been a number of reports of long-term dialysis patients developing carpal tunnel syndrome, in some bilateral (Delmez *et al.* 1982, Allieu *et al.* 1983, Emery *et al.* 1983). The patients tend to be middle-aged to elderly men. The incidence of the syndrome appears to be higher than in the general population (Spertini *et al.* 1984).

Anaemia

The almost invariable anaemia of chronic renal failure is multifactorial (*Lancet* 1983) and has two main components. Symptoms of anaemia cause considerable morbidity in dialysis patients. Whilst haemoglobin concentrations increase in time in some patients (Salahudeen *et al.* 1983), many have to live with an anaemia of around 6 g/dl. Transfusion temporarily improves symptoms but may lead to formation of cytotoxic antibodies which preclude transplantation. Anaemia is exacerbated by excessive blood sampling (Hocken & Marwah 1971), and the increased gut loss of blood (Rosenblatt *et al.* 1982) due to mucosa damage (Boyle & Johnston 1983) contributes to the anaemia.

Iatrogenic morbidity

Patients are dialysed against 360 to 800 litres of water weekly. Associations have been established between tap water containing trace quantities of aluminium, calcium, magnesium, copper, fluoride, sodium, bicarbonate, zinc, chloramines, nitrates or sulphates and dialysis toxicity (Friedman & Lundin 1982). Reference has already been made to the complex role of aluminium in renal osteodystrophy. Aluminium may in addition worsen the anaemia of dialysis patients (Touam *et al.* 1983) and accidental copper poisoning has been reported due to contamination of water used to prepare dialysate (Eastwood *et al.* 1983). Trace elements dialysed into the patient have no renal route of excretion and each dialysis contributes to cumulative poisoning.

Many drugs and their metabolites are renally excreted. The probability of an adverse reaction to many commonly used drugs is substantially increased even if there is only moderate renal failure (Jick 1977, Smith *et al.* 1966). The dialysis patient is at risk from incautious prescribing because bioavailability, volume of distribution and protein binding are all altered in uraemia (Avronoff 1983).

Conclusion

The outlook on dialysis is best for those patients who are normotensive, aged under 40 years at commencement and of extrovert or confident personality (Charra *et al.* 1983, Gutman 1983, Neff *et al.* 1983). Adverse factors include systemic disease and hypertensive nephrosclerosis. Hypertensive American or South African blacks fare poorly on haemodialysis (Gold 1980, Relman 1982). In addition, late referral of patients to a renal unit carries increased morbidity and mortality (Ratcliffe *et al.* 1984). Nevertheless, it is not clear why survival rates quoted in Table 1 vary so widely from 85% to 18% at ten years.

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