increased during treatment in all except case 1, and in case 4 pupillary light reflexes returned to normal.

The concentration of endotoxin and the activity of monocyte tissue thromboplastin were appreciably reduced during combined plasmapheresis and leucapheresis and during blood exchange treatment. C3d, which was present in the serum of all patients on admission, was not measurable after 24-48 hours of treatment. A similar reduction in endotoxin concentration and monocyte tissue thromboplastin activity during the first 24-48 hours in hospital was also observed, however, in patients with fatal meningococcal septicaemia not treated with apheresis.[5 9] C3d was not studied in these conventionally treated patients. This gradual reduction in endotoxin and monocyte tissue thromboplastin activity in patients not treated with apheresis or blood exchange may largely have been due to the binding of circulating endotoxin to cellular membranes with a subsequent reduction in monocyte stimulation. Hence the effect of combined plasmapheresis and leucapheresis cannot be evaluated by any of these laboratory variables.

One or more of the following factors may be responsible for the apparently successful effect of combined plasmapheresis and leucapheresis: (1) removal of plasma containing activated complement, activated clotting factors, and lysozymes secreted from activated granulocytes; (2) removal of activated and aggregated granulocytes, which excrete superoxide and hydroxy radicals and probably impair peripheral circulation[3]; (3) removal of activated monocytes exposing thromboplastin[5]; (4) removal of activated platelets with endotoxin attached; and (5) substitution of plasma factors by fresh frozen plasma. Concomitant vasodilatation may be less important; one patient (case 3) improved without such treatment.

Technically our study shows that both combined plasmapheresis and leucapheresis and blood exchange may be performed even in critically ill patients with hypotension and poor peripheral circulation. The transient circulatory collapse observed in case 2 was probably not due to the apheresis as a similar event was observed 12 hours later unrelated to such treatment. In conclusion, it seems justifiable to try combined plasmapheresis and leucapheresis or blood exchange transfusion in critically ill patients with meningococcal septicaemia. The future place of this treatment, however, must be determined by clinical trials. From our limited experience the plasma concentration of endotoxin and the monocyte tissue thromboplastin activity may be of prognostic value.

References

1 Bøvre K, Gedde-Dahl TW. Epidemiological patterns of meningococcal disease in Norway 1975-1979. *NIPH Ann* 1980;**3**:9-22.
2 Berild D, Gedde-Dahl TW, Abrahamsen T. Meningococcal disease in the Norwegian armed forces 1967-1979. *NIPH Ann* 1980;**3**:23-30.
3 Jacob HS. The role of activated complement and granulocytes in shock states and myocardial infarction. *J Lab Clin Med* 1981;**29**:645-90.
4 Østerud B, Eskeland T. The mandatory role of complement in the endotoxin-induced synthesis of tissue thromboplastin in blood monocytes. *FEBS Lett* 1982;**149**:75-9.
5 Østerud B, Flaegstad T. Increased tissue thromboplastin activity in monocytes of patients with meningococcal infection related to an unfavourable prognosis. *Thromb Haemost* 1983;**49**:5-7.
6 Schwartmann WB, Tillotson JR, Taft EG, Wright E. Plasmapheresis for meningococcemia with disseminated intravascular coagulation. *N Engl J Med* 1979;**300**:1277.
7 Østerud B, Bjørklid E. The production and availability of tissue thromboplastin in cellular populations of whole blood exposed to various concentrations of endotoxin. *Scand J Haematol* 1982;**29**:175-84.
8 Brandslund I, Siersted HE, Svehag SE, Teisner B. Double-decker rocket immunoelectrophoresis for direct quantitation of complement C3 split product with C3d specificities in plasma. *J Immunol Methods* 1981;**44**:63-71.
9 Harthug S, Bjorvatn B, Østerud B. Quantitation of endotoxin in blood from patients with meningococcal disease, using a limulus lysate test in combination with a chromogenic substrate. *Infection* 1983;**11**:192-6.

(*Accepted 14 November 1983*)

Late referral for maintenance dialysis

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Abstract

A study of patients accepted for maintenance dialysis at the Oxford renal unit in 1981 showed that 23 out of 55 patients were referred late, very shortly before the need for dialysis. This pattern of referral was associated with a higher morbidity at the start of dialysis which may have been preventable. In the late referral group 16 patients (70%) suffered major complications and three (13%) died; by contrast, in the early referral group three patients (9%) suffered complications and one died.

Early referral to a renal unit plainly benefits the patient and allows Health Service resources to be used more economically.

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Introduction

In a survey of patients in Britain dying of chronic renal failure the Medical Services Study Group of the Royal College of Physicians identified a group who died shortly after the start of dialysis,[1] and an accompanying leading article suggested that the deaths might have been due to late referral to specialist centres.[2] We have therefore reviewed the initial hospital morbidity and mortality and the type of dialysis in patients who began treatment for end stage renal failure in Oxford during 1981 classified according to whether they were referred early or late, late referral being defined as within one month before the start of dialysis.

Present study

PATIENTS

In all patients the decision to institute dialysis was based on uraemic symptoms associated with a creatinine clearance of less than 6 ml/min. Fifty five new patients started maintenance dialysis (24·4/million population). Their ages ranged from 17 to 70 years, and the modal age group was 50-59; 16 patients (29%) were over 55. Table I lists their renal diagnoses.

Thirty two patients (58%) referred more than one month before

dialysis had been attending the renal outpatient department for periods ranging from one month to 10 years (mean 4·1 years). The other 23 patients (42%) were referred late. All of these patients had a creatinine clearance of less than 6 ml/min at referral and either were suffering symptoms or suffered an onset of symptoms within one month. Seven patients with short histories were referred as soon as renal failure was diagnosed. In 15 patients renal disease had been diagnosed seven months to 13 years before referral. In 10 of these severe chronic renal failure (serum creatinine concentration >600 μmol/l (>6·8 mg/100 ml) serum urea >30 mmol/l (>180 mg/100 ml)) had been recognised, in two progression to severe uraemia had gone unrecognised during follow up, and in three there had been an important break in hospital attendance, during which renal failure had progressed. One patient with diabetes had been seen regularly for many years but chronic renal failure was first diagnosed only three weeks before referral.

MANAGEMENT

Early referral group—The appropriate dialysis for each patient—that is, haemodialysis in hospital or at home or continuous ambulatory peritoneal dialysis—was determined during outpatient management based on medical criteria and the patient's preference. Patients selected for haemodialysis were admitted electively for fashioning of an arteriovenous fistula. Twenty three patients (72%) were treated by haemodialysis via an arteriovenous fistula and two required temporary vascular access using subclavian catheters until their fistulas were satisfactory for dialysis. The remaining seven patients (22%) were selected for continuous ambulatory peritoneal dialysis.

TABLE I—*Causes of renal failure in all patients referred*

Early referral		Late referral	
Chronic glomerulonephritis	8	Chronic glomerulonephritis	8
Chronic pyelonephritis	7	Chronic pyelonephritis	2
Hypertension	5	Hypertension	3
Polycystic disease	6	Polycystic disease	1
Obstruction	1	Diabetes	4
Rapidly progressive glomerulonephritis	1	Obstruction	1
Myeloma	1	Rapidly progressive glomerulonephritis	1
Oxalate nephropathy	1	Hyperparathyroidism	1
Medullary cystic disease	1	Renal vein thrombosis	1
Systemic lupus erythematosus	1	Amyloidosis	1

For 29 patients (91%) the first dialysis was arranged during outpatient visits before the onset of serious uraemic complications. Patients treated by haemodialysis stayed overnight after their first treatment and were then discharged to attend as hospital outpatients or for training at home. Patients treated by continuous ambulatory peritoneal dialysis stayed in hospital for the training period.

Late referral group—Fourteen patients (61%) were treated from the outset by continuous ambulatory peritoneal dialysis using a soft catheter implanted in the operating theatre. Peritoneal dialysis subsequently failed in three patients, who were transferred to haemodialysis. Three patients who needed urgent haemodialysis for severe pulmonary oedema were subsequently changed to continuous ambulatory peritoneal dialysis for medical or social reasons. The remaining six patients (26%) were treated by haemodialysis using either arteriovenous shunts or subclavian catheters while their arteriovenous fistulas matured.

Results

Serious complications which prolonged the stay in hospital at the start of dialysis were present in three patients (9%) in the early referral group and 16 (70%) in the late referral group $\chi^2 = 18{\cdot}86$ ($p < 0{\cdot}001$). Table II gives the nature of these complications together with age, renal diagnosis, and time of referral. The most common complications were pulmonary oedema (12 patients), pericarditis (seven), and severe hypertension (four). Table III groups the patients according to age, renal diagnosis, and mode of dialysis, the confounding bias due to each of these variables being corrected with the Mantel-Haenszel test.[3] After correction a highly significant difference in outcome ($p < 0{\cdot}001$) between early and late referral groups remained for all variables.

Only four deaths occurred, one in the early referral group and three in the late group. These small numbers were not analysed.

Discussion

The number of new patients accepted for maintenance dialysis in Oxford each year is similar to that in other British centres but roughly half the rate in comparable European countries.[4] This difference is due to fewer elderly patients being given dialysis in Britain[5] despite the detection of these

TABLE II—*Patients suffering complications during stay in hospital at start of dialysis*

Case No	Age (years)	Period between referral and dialysis	Renal diagnosis	Pre-existing non-renal disease	Complications
				Early referral	
1	20	15 months	Systemic lupus erythematosus		Blood pressure 230/130 mm Hg. Nephrotic with pulmonary oedema. Taking steroids and cyclophosphamide
2	30	12 months	Chronic glomerulonephritis	Splenectomy for idiopathic thrombocytopenic purpura	Pneumonia with pneumococcal septicaemia and cardiac arrest. Successful resuscitation
3	50	5 years	Chronic pyelonephritis	Chronic rheumatic aortic and mitral valve disease	Pericarditis and pulmonary oedema. Death from heart failure
				Late referral	
4	59	<1 day	Diabetic glomerulosclerosis	Diabetes mellitus and hypothyroidism	Coma, hypothermia (temperature 31·0°C), lactic acidosis, Gram negative septicaemia
5	18	<1 day	Chronic glomerulonephritis		Uraemic with disequilibrium and convulsions after first haemodialysis
6	31	<1 day	Malignant hypertension		Hypertensive encephalopathy (blood pressure 250/160 mm Hg) and pulmonary oedema
7	62	<1 day	Chronic glomerulonephritis		Pulmonary oedema and pericarditis
8	51	<1 day	Chronic glomerulonephritis		Uraemic and hypertensive (blood pressure 240/130 mm Hg) encephalopathy with convulsions. Pulmonary oedema. Supraventricular tachycardia. Probable myocardial infarction
9	50	<1 day	Malignant hypertension		Pulmonary oedema, pericarditis, and haematemesis
10	51	<1 day	Rapidly progressive glomerulonephritis		Uraemic and hypertensive (blood pressure 230/130 mm Hg) encephalopathy. Pulmonary oedema
11	54	<1 day	Retroperitoneal fibrosis		Pulmonary oedema, supraventricular tachycardia, and gastrointestinal haemorrhage
12	60	<1 day*	Chronic pyelonephritis	Cerebrovascular disease	Pulmonary oedema. Minor cerebrovascular accident
13	40	<1 day	Chronic glomerulonephritis		Pericarditis. Acute myocardial infarction
14	55	1 day	Amyloidosis	Spina bifida, chronically infected pressure sores	Pericarditis with cardiac tamponade. Death from bronchopneumonia
15	45	2 days	Bilateral renal vein thrombosis		Gastrointestinal and retroperitoneal haemorrhage (taking anticoagulants)
16	50	3 days	Diabetic glomerulosclerosis	Diabetes mellitus	Hypertension (blood pressure 230/130 mm Hg) and pulmonary oedema
17	56	3 days	Chronic pyelonephritis	Transverse myelitis, paraplegia with spastic bladder	Fatal myocardial infarction
18	70	2 weeks	Hyperparathyroidism		Pulmonary oedema and pericarditis
19	32	3 weeks	Diabetic glomerulosclerosis	Diabetes mellitus, gluten sensitive enteropathy	Pulmonary oedema and pericarditis. Haemothorax after pleural aspiration. Death from sepsis

*Peritoneal dialysis via temporary catheter instituted shortly before referral.

TABLE III—*Referral pattern (E = early, L = late) and complications at start of dialysis*

	Referral	Hospital course: Uncomplicated	Hospital course: Complicated	χ^2
(*a*) All patients	E	29	3	18·86
	L	7	16	
(*b*) Renal diagnoses:				
Chronic glomerulonephritis	E	7	1	18·04
	L	4	4	
Chronic pyelonephritis	E	6	1	
	L		2	
Hypertension	E	5		
	L	1	2	
Polycystic disease	E	6		
	L	1		
Diabetes	E			
	L	1	3	
Other	E	5	1	
	L		5	
(*c*) Age (years):				
< 55	E	22	3	23·69
	L	4	10	
⩾ 55	E	8		
	L	2	6	
(*d*) Initial mode of dialysis:				
Haemodialysis	E	23	2	18·21
	L	3	6	
Peritoneal dialysis	E	6	1	
	L	4	10	

Statistical—(*a*) All patients: $\chi^2 = 18{\cdot}86$, $p < 0{\cdot}001$. (*b*) Correction for confounding bias due to effect of renal diagnosis on referral pattern: $\chi^2 = 18{\cdot}04$, $p < 0{\cdot}001$. (*c*) Correction for effect of age on referral pattern: $\chi^2 = 23{\cdot}69$, $p < 0{\cdot}001$. (*d*) Correction for association between referral pattern and initial mode of dialysis: $\chi^2 = 18{\cdot}21$, $p < 0{\cdot}001$.

patients in surveys of uraemia in the population[6 7] and reported successful treatment in this age group.[8]

In our series patients with polycystic kidney disease were mostly referred early. In this disorder diagnosis is often made at an early stage, many patients are detected during family studies by renal units, and progress to end stage renal failure is predictable over several decades. For most other chronic renal diseases the diagnosis of renal failure is often delayed and progression to end stage may be unpredictable initially. All four diabetics and some older patients were referred late, perhaps owing to uncertainty about their suitability for dialysis. Arguably some of the excess morbidity suffered by the late referral group was accountable by differences between groups in terms of renal diagnosis, age, type of dialysis, and other, less readily definable variables. A randomised prospective study will never be available to answer this question, but after correction for confounding bias due to these readily definable variables, a very highly significant difference in outcome ($p < 0{\cdot}001$) between early and late referral groups remained, suggesting a specific effect of referral pattern.

Late referral is associated both with complications attributable directly to a delay in dialysis, such as pulmonary oedema, severe hypertension, pericarditis, and encephalopathy and with those occurring secondarily in very ill patients, such as gastrointestinal haemorrhage, myocardial infarct, and sepsis. Dialysis was often an emergency procedure with haemodialysis an essential treatment for severe pulmonary oedema. In other patients referred late insertion of a soft catheter in the operating theatre followed by continuous ambulatory peritoneal dialysis was an important initial mode of dialysis because it avoided the need for immediate vascular access. Haemodialysis required temporary vascular access procedures until an arteriovenous fistula matured. As a consequence of late referral some patients underwent several changes in mode of dialysis, which further prolonged the period in hospital.

Although it has been stated that progression of the renal failure is almost always predictable by extrapolation of a plot of the reciprocal of the serum creatinine concentration against time,[9] a survey in Oxford pointed out the wide variation in concentrations of serum creatinine at which uraemic symptoms develop and furthermore noted a terminal acceleration in the rate of rise in 36% of patients, which was usually inexplicable.[10]

To allow for these difficulties and ensure referral before the onset of uraemic complications we recommend referral of patients when the serum creatinine concentration reaches about 600 μmol/l (6·8 mg/100 ml) or the creatinine clearance falls below 10 ml/min. For patients with less severe renal failure a plot of the reciprocal of serum creatinine values against time will usually provide a rough guide to the rate of progression. In our retrospective survey reasons for delayed referral could not be accurately assessed for individual patients, but probable reasons included attempts to treat a correctable factor, unwillingness of the patient or doctor to contemplate renal replacement while the patient was in good health, and doubt about suitability for dialysis. This last possibility is of particular concern, as accurate assessment is often impossible after the onset of uraemic complications, and we particularly recommend early referral of patients with other systemic disease.

It is possibly not surprising that late referral is associated with a high complication rate. What is important is that these complications were virtually eliminated from our early referral group, the vast majority even of the older patients beginning dialysis smoothly. In addition to averting uraemic complications, early referral to renal units allows physical and mental preparation before treatment. Management includes optimal treatment of hypertension, anaemia, and renal osteodystrophy and careful conservation of peripheral vessels and the peritoneal cavity, essential for haemodialysis and continuous ambulatory peritoneal dialysis. The type of dialysis—either haemodialysis in hospital or at home or continuous ambulatory peritoneal dialysis—is decided during outpatient management, and for patients allocated to haemodialysis an arteriovenous fistula is fashioned well before the need for dialysis. Preparations for home dialysis may be undertaken before treatment. Early referral also allows assessment for renal transplantation and search for a related donor; and there is the possibility of transplantation with a cadaver kidney before dialysis.

There were too few deaths in this study to determine whether early referral affects mortality; nevertheless, by early referral to renal units morbidity due to uraemic complications is reduced and expensive health resources are used more economically.

We are grateful to Dr C K McPherson, Oxford, who advised on the statistical analysis of these data.

References

1 Medical Services Study Group of the Royal College of Physicians. Death from chronic renal failure under the age of 50. *Br Med J* 1981;**283**: 283-6.

2 Anonymous. Audit in renal failure: the wrong target? [Editorial.] *Br Med J* 1981;**283**:261-2.

3 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**:719-48.

4 Jacobs C, Broyer M, Brunner FP, *et al.* Combined report on regular dialysis and transplantation in Europe, XII, 1980. *Proc Eur Dial Transplant Assoc* 1981;**18**:2-58.

5 Brynger H, Brunner FP, Chantler C, *et al.* Combined report on regular dialysis and transplantation in Europe, XI, 1979. *Proc Eur Dial Transplant Assoc* 1980;**17**:2-86.

6 Branch RA, Clark GW, Cochrane AL, Jones JH, Scarborough H. Incidence of uraemia and requirements for maintenance haemodialysis. *Br Med J* 1971;i:249-54.

7 McGeown MG. Chronic renal failure in Northern Ireland, 1968-70: a prospective survey. *Lancet* 1972;i:307-10.

8 Taube DH, Winder EA, Ogg CS, *et al.* Successful treatment of middle aged and elderly patients with end stage renal disease. *Br Med J* 1983; **286**:2018-9.

9 Mitch WE, Walser M, Buffington GA, Leman J. A simple method of estimating progression of chronic renal failure. *Lancet* 1976;ii:1326-8.

10 Ledingham JGG, Hart G. The optimum time to start regular haemodialysis. In: Davison AM, ed. *Dialysis review.* Tunbridge Wells: Pitman Medical, 1978:22-31.

(*Accepted 15 November 1983*)