Occasional Review

Why do patients with lupus nephritis die?

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Abstract

Over 20 years 42 of 138 patients with systemic lupus erythematosus "died"—that is, suffered actual death or went into terminal renal failure, or both; data from 41 were available for analysis. In most patients the causes of death were multiple. Twenty seven patients went into terminal renal failure, of whom 25 were offered dialysis treatment. Three regained renal function later, 12 survived on dialysis or with functioning kidney allografts—almost all with inactive lupus—but 13 died after starting dialysis, most within a few weeks or months. The principal causes were active lupus or infection. In those patients with renal failure after rapid deterioration in renal function ($n=14$) there were nine deaths, while of 10 patients with a slow evolution into renal failure, only four died.

Four patients with impaired and 10 with normal renal function died, again most often from complications of lupus or from infection. Vascular disease was a major cause of death in seven patients, all but two of whom were young; of 15 postmortem examinations, eight showed severe coronary artery atheroma, and three surviving patients required coronary bypass operations. Analysis of the timing of death or entry into renal failure showed that in 12 out of 13 patients who died within two years of onset the lupus was judged to be active, while this was true in only eight out of 19 patients who died later. Six of the seven vascular deaths occurred later than two years from onset, while only nine of 26 renal "deaths" occurred before two years; deaths from infections ($n=13$) were distributed equally. Despite this and aggressive treatment of active disease, the principal cause of actual death was uncontrolled lupus.

Introduction

There is considerable information on causes of death in systemic lupus erythematosus.¹⁻¹⁶ Even in series reporting the whole range of lupus, with or without evident renal disease, renal failure emerges as an important cause of death. Equally, patients with lupus nephritis may fall victim to other manifestations of lupus, to complications of treatment, or to associated features such as vascular disease. The problem has been complicated further by the availability of substitution therapy for renal failure in the form of dialysis and trans-

plantation. Patients surviving renal failure of lupus nephritis remain at risk from fatal disease in other organs caused by the lupus. Thus even though we have data on causes of death in lupus, many of these data do not apply to patients with nephritis as the principal clinical feature, and the impact of substitution therapy has been taken into account in very few series.

The fate of patients requiring renal replacement therapy because of lupus nephritis has been described,¹⁷⁻²¹ and we have detailed our own experience elsewhere.²² The purpose of this paper is to examine the overall pattern of mortality in our patients suffering from lupus, all of whom had prominent renal disease, in order to assess the relative roles of extrarenal lupus and complications of treatment in determining mortality when compared with renal failure itself.

Patients and methods

Between 1964 and 1982, 138 patients with systemic lupus erythematosus were referred to the renal unit at Guy's Hospital. All satisfied the preliminary (1971) and 1982 criteria of the American Rheumatism Association²³ and all had on at least one occasion (usually many) a positive antinuclear factor preparation or a raised binding capacity for double stranded DNA, or both, in serum. All had clinical evidence of nephritis, with proteinuria or abnormalities of the urinary sediment, and all had undergone renal biopsy at some time yielding histological evidence of lupus nephritis. After assessment and planning of treatment some of the patients returned to the care of the referring centre, but most were followed up in the renal unit, either solely or jointly with the referring physician.

During follow up, varying from two to 22 years (mean 8.4 years), 42 of the patients (30.4%) either died or entered end stage renal failure, events which together are referred to as "death" (since patients reaching end stage renal failure would have died but for substitution therapy, so that the patients who in fact survived by virtue of dialysis or transplantation were for actuarial analysis regarded as dead). One patient was excluded from the study because there was insufficient information on her death, which occurred elsewhere.

CAUSES OF DEATH

Since in nearly all cases death resulted from several factors, we did not attempt to ascribe a single main cause for each patient. Instead we classified the causes of death under six headings.

Active generalised lupus was defined as progressive spread of the disease to several systems, causing severe dysfunction with immunological or histological evidence of disease activity.

Active lupus, single organ was defined as progressive spread of the disease to affect one major organ, causing severe dysfunction without evidence or with only minor disruption of other systems, with immunological or histological evidence of disease activity.

Inactive lupus was defined as evidence of previous organ damage causing dysfunction but with no signs of continuing clinical or immunological activity at the time of death.

Vascular was defined as clinical or histological evidence of major life threatening occlusion of coronary, cerebral, or peripheral circulation.

Infection was defined as major infection(s) which contributed to or caused the death of the patient.

Other, unrelated was defined as other causes of death not related to systemic lupus erythematosus or its treatment.

Disease of the kidney caused by systemic lupus erythematosus presents a

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TABLE 1—Patients still alive by virtue of substitution therapy for renal failure

Case No	Age at ESRF (years)	Time to ESRF:		Renal substitution therapy*	Lupus activity at ESRF		Renal function deterioration‡	Remarks
		From diagnosis	From first renal manifestation		Renal†	Extrarenal‡		
1	46	3 yr 6 mo	3 yr	HD 3 years; Tx 2 years	—B	—	C	Renal vein thrombosis just before ESRF
2	19	5 yr	5 yr	HD 2 months; Tx 10 days; CAPD 10 months; Tx 1 year 9 months	—B	LT positive	C	Tricuspid valve removed for recurrent endocarditis on dialysis
3	37	2 yr 8 mo	2 yr 8 mo	HD 3 weeks; Tx 1 year 8 months	—B	—	C	Man: bilateral Achilles tendon rupture before ESRF
4	28	8 yr	4 yr	HD 3·5 months; Tx 10 months	—	—	C	Multiple venous thromboses but no "lupus" anticoagulant
5	12	1 yr	1 mo	HD 7 months; Tx 11 days; HD 5 months; Tx 16 days; HD 3 years 10 months	+B	CNS, skin, LT positive	A	
6	40	6 mo	5 mo	HD 1·5 months; Tx 5 weeks; HD 2 months; CAPD 2 months	+B	Lung, CNS, LT positive	A	
7	33	7 yr	7 yr	HD 15 months	—B	LT positive	C	Interstitial nephritis before ESRF. Coronary bypass surgery on dialysis
8	40	2 mo	2 mo	HD 14 months	+B	Skin, joints, LT positive	A	
9	39	3 yr	3 yr	HD 3 years	+B	LT positive	?	No data available to assess rate of functional deterioration
<i>Patients who recovered renal function</i>								
10	22	9 yr	9 yr	HD 14 months; R 6 months; CAPD 3 years 2 months	+B	Lung, skin, joints, LT positive	A	
11	52	4 yr 5 mo	4 yr 5 mo	CAPD 4 months; R 7 months	—B	LT positive	C	Current renal function: plasma creatinine 450 µmol/l (5·0 mg/100 ml)
12	21	6 mo	6 mo	HD 1·5 months; R 3 months	+B	LT positive	A	Current plasma creatinine 12 µmol/l (0·1 mg/100 ml), glomerular filtration rate 65 ml/min

ESRF=End stage renal failure.

*HD=Haemodialysis. Tx=Transplantation. CAPD=Continuous ambulatory peritoneal dialysis. R=Recovery of function.

†—=Inactive lupus nephritis. +=Active lupus nephritis. B=Biopsy proved.

‡LT=Lupus tests (DNA binding, C3, C4). CNS=Central nervous system.

§C=Chronic deterioration. A=Acute deterioration before ESRF.

special problem in classifying causes of death because of the possibility of replacement therapy. *Lupus nephritis* (classified as above) was considered as a cause of death if the patient died within one month of reaching end stage renal failure, by which time the effects of renal failure would not have been corrected in a stable fashion by dialysis or transplantation.

ACTIVITY OF SYSTEMIC LUPUS ERYTHEMATOSUS BEFORE AND AT DEATH

In analysing the activity of systemic lupus erythematosus before and at entry into end stage renal failure renal damage by systemic lupus erythematosus was considered similarly to active lupus affecting other organs.

Clinically "active" lupus nephritis was recorded as present if there was (a) proteinuria or active urinary sediment with (b) extrarenal manifestations of lupus activity, even if minor and not life threatening, such as skin or joint disease, together with (c) immunological or histological evidence of activity.

Histological appearances of renal biopsy or necropsy specimens were judged to be "active" when fresh cellular crescents, diffuse or focal active proliferation of endocapillary cells, tuft necrosis, capillary thrombosis, or vasculitis was visible.

Immunological evidence of disease activity was defined as low serum concentrations of C3 (<55% normal) and C4 (<50% normal), a raised binding titre of serum deoxyribonucleic acid (>30 µm), or (when available) the presence of excess amounts of immune complex like material in the serum.

RATE OF DETERIORATION IN RENAL FUNCTION

For analysis the patients were divided into (a) those with *rapid* deterioration in renal function, defined as a fall in glomerular filtration rate of 40 ml/min or more or a rise in plasma creatinine concentration of 500 µmol/l (5·7 mg/100 ml) or more in the three months before end stage renal failure, and (b) those with *slow* deterioration if less than this.

TIMING OF "DEATH"

Patients who suffered true death or went into end stage renal failure were divided into those with *early* death or renal failure, defined as occurring less than two years after onset of systemic lupus erythematosus, and those with *late* death, when the interval was greater than this.

STATISTICAL

Analysis of dependency in two way tables was performed using the G test with Yates's correction for small samples.²⁴

Results

There were 36 female and five male patients in the study, with a mean age at death of 35·8 years (range 11–63). Those who went into renal failure but did not die were of almost identical age (mean 35·4 years; range 11–63). Eight were of West Indian origin, two west African, two Arab, two Chinese, one Pakistani, one Iranian, one Greek, and 24 of resident British stock.

FINDINGS AT AND BEFORE DEATH OR RENAL FAILURE

Tables I and II show the circumstances of "death" of the 41 patients. Twelve patients (cases 1–12; table I) who went into end stage renal failure received renal substitution therapy and survived. Of these, at last follow up four had functioning renal cadaveric allografts, six were receiving dialysis, and two (cases 11 and 12) had recovered sufficient renal function to survive without dialysis; one patient (case 10) had a temporary recovery of renal function.

Fifteen patients (cases 13–27) went into end stage renal failure and subsequently died (table II). Two (cases 13 and 14) were not offered substitution therapy; one was paraplegic and the other demented. The remaining 13 patients began dialysis. Three patients (cases 24, 26, and 27) died after more than one month of dialysis, and the other 10 died within one month of beginning dialysis, most commonly from active lupus. The remaining 14 patients (cases 28–41; table II) died from extrarenal causes, 10 with normal or near normal renal function (cases 32–41) and four with moderate chronic renal failure.

Tables III and IV analyse the causes of the true deaths in detail. In the 10 patients who died shortly after beginning treatment for end stage renal failure (cases 15–23 and 25) the causes of death were mainly active systemic lupus erythematosus and infection. The three patients who died more than one month after beginning treatment did so because of recurring manifestations of lupus in the central nervous system after three months of haemodialysis (case 24), gastrointestinal bleeding during a rejection episode one and a half months after transplantation and an initial month on haemodialysis (case 26), and myocardial infarction five years after transplantation, with good graft function (case 27). Infection was the single commonest cause of death in those with functioning kidneys (table IV).

ANALYSIS OF DEATHS IN RELATION TO COURSE OF DISEASE

Causes of "death" as classified in tables I–III were analysed in terms of the duration of the disease and the effect on the kidneys (renal versus non-renal deaths). Table V summarises the causes of death in patients dying within two years of onset (early deaths) and those who died later (late deaths). The totals were in both categories greater (56 in all) than the number of patients, since in many the causes were multiple. In the 17 early deaths active systemic lupus erythematosus (12 cases) and infection (eight cases) predominated. In

the 24 late deaths, although active systemic lupus erythematosus was still prominent (eight cases), vascular deaths became important (six). Statistical analysis showed that active systemic lupus erythematosus was significantly more common ($p < 0.05$) in early than in late deaths, but no other differences reached significance. Deaths from renal causes were also commoner in the late group, but this also did not reach significance at the 5% level.

Analysis of the timing of the main categories of "death" after diagnosis (fig) showed that the number of deaths decreased progressively with time. This reflected not only a fall off in the number of patients at risk (fig) but also a real decrease in mortality with time.

Clinical circumstances of entering end stage renal failure were correlated with outcome in patients offered renal substitution therapy. Table VI summarises the activity of systemic lupus erythematosus, renal histology, treatment, and outcome according to the rate of deterioration of renal function in the three months preceding end stage renal failure. One patient (case 9) had to be excluded from this analysis because there were insufficient data to assess the rate of decline in her renal function. The mortality among those with a rapid decline in renal function and active systemic lupus erythematosus at end stage renal failure (14 patients) was high (64%), whereas those with a slow decline and inactive lupus (10 patients) did better (40% mortality). This difference just failed to reach significance at the 5% level.

TABLE II—Clinical details of patients who suffered true death

Case No	Age at death (years)	Age at ESRF (years)	Time to ESRF or death:		Renal function at death*	Renal substitution therapy†	Lupus activity at ESRF		Renal function deterioration‡
			From diagnosis	From first renal manifestation			Renal†	Extra-renal‡	
Not offered renal substitution therapy									
13	40	40	3 yr 9 mo	1 yr 10 mo	ESRF	—	—	—	C
14	58	58	6 yr 4 mo	6 yr 4 mo	ESRF	—	—	LT negative	C
Offered renal substitution therapy but died									
15	63	63	2 yr 9 mo	5 mo	ESRF	PD 10 days	+B	Pleuritis	A
16	56	56	16 yr	8 yr	ESRF	PD 1 week	+PM	CNS, lung, liver	A
17	42	42	3 yr	1 yr	ESRF	HD 1 month	+B	Skin, LT positive	A
18	11	11	1 yr 6 mo	1 yr	ESRF	HD 2 weeks	+	Pleuritis, LT positive	A
19	29	29	6 mo	4 mo	ESRF	HD 1 month	+B	Coagulation, LT	A
20	42	42	1 yr	3 yr	ESRF	PD 4 days	+B	Skin, LT	A
21	35	35	1 yr 9 mo	1 yr 9 mo	ESRF	PD 2 days	?	No, No LT	A
22	47	47	9 yr 6 mo	2 yr	ESRF	PD 2 days	—PM	No, LT negative	A
23	40	40	2 yr	2 yr	ESRF	PD 16 days	—B	—	C
24	24	24	3 mo	2 mo	ESRF	HD 3 months	+B	Pleuritis, LT positive	A
25	19	19	9 yr	9 yr	ESRF	HD 1 week	—	—	C
26	16	16	3 yr	3 yr	Tx rejection	HD 1 month; Tx 1·5 months	—B	—	C
27	33	28	6 yr	4 yr	Creatinine 160 μ mol/l (1·8 mg 100 ml)	HD 1 month; Tx 5 years	—	—	C
Death from non-renal causes with functioning kidneys									
28	42	—	8 yr	5 yr	CRF	—	—	—	C
29	25	—	1 yr	1 yr	CRF	—	—	—	A
30	38	—	4 yr 10 mo	4 yr 10 mo	CRF	—	—	—	C
31	56	—	9 yr	7 yr	CRF	—	—	—	C
32	22	—	1 yr 1 mo	1 yr 1 mo	Normal	—	—	—	—
33	63	—	5 yr	4 yr	Normal	—	—	—	—
34	41	—	1 yr 1 mo	3 mo	Normal	—	—	—	—
35	16	—	3 yr 9 mo	3 yr	Normal	—	—	—	—
36	27	—	6 mo	6 mo	Normal	—	—	—	—
37	17	—	10 mo	10 mo	Normal	—	—	—	—
38	12	—	1 yr	1 yr	Normal	—	—	—	—
39	27	—	8 yr	5 yr	Normal	—	—	—	—
40	42	—	4 mo	4 mo	Normal	—	—	—	—
41	39	—	1 yr 6 mo	1 yr 6 mo	Normal	—	—	—	—

ESRF = End stage renal disease.

*Tx = Transplant transplantation. CRF = Chronic renal failure.

†PD = Peritoneal dialysis. HD = Haemodialysis.

‡+ = Active lupus nephritis. — = Inactive lupus nephritis. B = Biopsy proved. PM = Postmortem confirmation.

§LT = Lupus test (DNA binding, C3, C4). CNS = Central nervous system.

||C = Chronic deterioration. A = Acute deterioration.

TABLE III—Causes of true death among patients in renal failure

Case No	Necropsy	Lupus			Other			Remarks
		Active generalised lupus	Active single organ lupus	Inactive organ lupus	Infection	Vascular	Other unrelated	
13	—	—	—	CNS	—	—	—	Paraplegia from transverse myelitis previously
14	—	—	—	—	—	+	—	Man: generalised vascular disease (angina, left ventricular dysfunction, claudication, cerebral degeneration)
15	+	CNS, kidney	—	—	+	—	—	Multiple small infarcts in pons and cerebellum; lobar pneumonia; staphylococcal septicaemia; peritonitis
16	+	CNS, lung, liver, kidney	—	—	—	—	—	Interstitial pneumonia; liver failure; inflammatory infiltration of portal tracts and fatty changes; severe CNS demyelination
17	+	Lung, liver, CNS, kidney	Kidney	—	+	—	—	Bilateral fungal pneumonia; fungal myocarditis; CNS fungal abscesses
18	+	—	—	—	—	—	—	Lung: vasculitis and alveolar haemorrhage; liver: fatty changes and inflammatory infiltration; CNS: vasculitis and necrosis
19	—	Coagulation, kidney	—	—	—	—	+	Recent lower limb arterial thrombosis with foot gangrene; gastrointestinal bleeding after streptokinase
20	—	Liver, kidney	—	—	—	—	—	Liver failure: hepatic infiltration and intrahepatic cholestatic picture on liver biopsy
21	+	—	—	Kidney	+	+	—	Pyogenic lung and brain abscesses; recent myocardial infarction (necropsy histology not available)
22	+	—	—	Lung, kidney	—	—	+	Profound hypotension during cardiac catheterisation for investigation of right sided heart failure leading to acute renal failure; infarction of small bowel with haemorrhage; acute tubular necrosis; pulmonary hypertension
23	+	—	—	Kidney	+	—	—	Tuberculosis of lung, intestines, and lymph nodes; lobar pneumonia, septicaemia
24	—	—	CNS	—	—	—	—	CNS lupus; patient well dialysed
25	+	—	—	—	—	+	—	Severe triple vessel coronary atheroma plus massive left ventricular infarct
26	—	—	—	—	—	—	+	Man: gastrointestinal bleeding with coagulation abnormalities during prolonged, uncontrollable rejection
27	—	—	—	—	—	+	—	Sudden death; angina, myocardial infarction, and severe coronary atheroma: good transplant function

CNS = Central nervous system.

FOLLOW UP IN RENAL FAILURE

The 15 patients who survived the period immediately after end stage renal failure were followed up for a total of 36 patient years (mean 2.4 years; range 2.5 months to 5.0 years). Ten patients were dialysed for more than three consecutive months for a total of 233 patient months (mean 23 months; range 3.5 to 58 months).

Persistent or recurring active extrarenal systemic lupus erythematosus was not a major problem in patients surviving end stage renal failure. Of the six patients who had active disease before starting dialysis, only one died (elsewhere) from recurrent manifestations of lupus in the central nervous system and three patients had exacerbations (cutaneous and minor neurological), easily controlled by a temporary increase in immunosuppression and mainly during the first year of dialysis. Only one of the patients who had inactive lupus at end stage renal failure later had recurrent activity (case 1: episode of arthritis with depressed complement values and raised DNA binding titre after two years of haemodialysis). All patients receiving dialysis were maintained with small doses of prednisone (5-15 mg/24 h) and azathioprine (1-2 mg/kg/24 h). Three patients were able to discontinue dialysis (cases 10 to 12), although in one (case 10) dialysis was reinstituted after 32 months and another (case 11) again went into terminal uraemia.

TABLE IV—Causes of true death among patients with functioning kidneys

Case No	Necropsy	Lupus			Other			Remarks
		Active generalised lupus	Active single organ lupus	Inactive organ lupus	Infection	Vascular	Other unrelated	
28	—	—	—	—	+	+	—	Lobar pneumonia; septicaemia (<i>Klebsiella pneumoniae</i>); severe ischaemic left ventricular dysfunction
29	—	—	—	—	+	—	—	Gram negative septicaemia; active lupus nephritis but death before ESRF
30	—	—	—	—	—	+	—	Insulin dependent diabetes; diabetic and lupus nephropathy; several cerebrovascular accidents proved angiographically
31	+	Liver, lung, gastrointestinal tract, kidney	—	—	+	—	—	Generalised varicella; liver failure—cirrhosis and active vasculitis; lung infarction and vasculitis; gastrointestinal vasculitis
32	+	—	—	—	+	—	—	Bilateral pneumonia, cerebellar abscesses; pneumococcal meningitis
33	+	—	—	+ Lung	—	+	+	Severe liver necrosis (?rifampicin); recent myocardial infarction; fibrosing pneumonitis; pulmonary tuberculosis
34	+	Lung, liver, CNS	—	—	+	—	—	Alveolar haemorrhage and lung vasculitis; hepatic fatty change with portal tract infiltration; Gram negative septicaemia
35	+	—	Coagulation	—	—	—	—	Massive bilateral pulmonary emboli while receiving heparin for deep vein thrombosis
36	—	—	Lung	—	+	—	—	Probable progressive fibrosing pneumonitis; Gram negative septicaemia
37	—	—	—	—	+	—	—	Pulmonary sepsis with active (cutaneous and articular) lupus and near normal renal function
38	—	—	—	—	+	—	—	Meningococcal septicaemia with meningitis
39	+	CNS, liver, heart	—	—	—	—	—	CNS; lupus myocarditis causing severe left ventricular dysfunction; liver failure—hepatic inflammatory infiltration
40	—	—	CNS	—	+	—	—	Aspergillus pneumonia; progressive cord and cerebellar signs
41	—	—	CNS	—	—	—	—	CNS lupus

CNS=Central nervous system. ESRF=End stage renal failure.

TABLE V—Major causes of “death” in patients dying within two years (early) and later than two years (late)

		State of lupus		Other		
		Active	Inactive	Vascular	Infection	Other unrelated
Early “deaths” (n=17)						
Deaths from non-renal causes (n=8)		4			7	
“Deaths” from renal causes (n=9)	{ 4 at ESRF 1 after ESRF* 4 alive	3 1 4	1	1	1	1
Total		12	1	1	8	1
13						
Late “deaths” (n=24)						
Deaths from non-renal causes (n=6)		3	1	3	2	1
“Deaths” from renal causes (n=18)	{ 7 at ESRF 3 after ESRF† 8 alive	3 3 2	4 4 6	1 2	3	2
Total		8	11	6	5	3
19						

ESRF=End stage renal failure.
*Patient reached ESRF due to active lupus nephritis.
†Patients reached ESRF with inactive lupus.

TRANSPLANTATION

Eight patients received 10 kidney allografts. Two patients died one and a half months and five years after transplantation (cases 26 and 27); two patients returned to dialysis (one (case 5) after acutely rejecting two kidneys and the other (case 6) after rejecting one); and four patients (cases 1 to 4) had normal graft function 24, 21, 20, and 10 months after transplantation. Systemic lupus erythematosus was inactive after transplantation: in particular there was no evidence of recurrent lupus nephritis in the grafts. All patients received maintenance immunosuppressive treatment with prednisone (10-15 mg/24 h) and azathioprine (2.5 mg/kg/24 h).

VASCULAR DISEASE

Vascular disease as a cause of death in seven patients (cases 14, 21, 25, 27, 28, 30, and 33)—that is, 24% of the total number of true deaths. Death resulted from coronary artery disease in five patients (myocardial infarction documented at necropsy in four, severe ischaemic left ventricular dysfunction proved by gated isotopic cardiac scan in one (case 28)); cerebrovascular accidents (proved arteriographically) in one (case 30; this patient also had insulin dependent diabetes mellitus and diabetic nephropathy); and generalised vascular disease in one (case 14).

Three of these patients were women aged under 40 (cases 21, 27, and 30) and one a man of 19 (case 25). Necropsy disclosed severe coronary atherosclerosis in four further patients dying from other causes, one of them (case 22) aged 47. Of the 15 necropsies, moderate to severe atheroma affecting the coronary arteries was found in eight.

Reviewing our series of patients with systemic lupus erythematosus who survived with renal function we identified a further seven with serious

vascular disease. Three of them were young women (aged 33, 35, and 38 years) with severe angina, three of them having required coronary bypass grafting, including one receiving haemodialysis. We could not detect a constant pattern of presence of risk factors (duration and severity of hypertension, raised serum lipid values, prolonged nephrotic syndrome, duration and dose of corticosteroid treatment) or associated heart disease (endocarditis or pericarditis) in the group of six patients with severe ischaemic heart disease below the age of 40 (date not shown), but detailed comparison with age matched patients with lupus and healthy controls was not performed.

Conclusions and discussion

A principal finding in this study was of a group of patients (10 out of the total of 25) who died very soon despite beginning dialysis.²² With two exceptions they reached terminal renal failure after a phase of rapidly declining renal function. In most this seemed to be due to active lupus nephritis, although other haemodynamic factors may have contributed to the rapid deterioration in glomerular filtration rate.

The patients who survived the period immediately after end stage renal failure fared relatively well, and the few who had active lupus at that stage experienced progressively fewer extrarenal manifestations while receiving low doses of corticosteroids and azathioprine as maintenance treatment. The rare “flares” of active disease were easily controlled. There were three deaths in this group, but only one was due to a recrudescence of lupus, again shortly after end stage renal failure.

TABLE VI—Lupus activity, treatment, and outcome according to deterioration in renal function before end stage renal failure (ESRF)

Cause of deterioration	No of patients	Lupus activity at ESRF	Renal histology at ESRF	Immuno-suppression before ESRF	Outcome
<i>Acute deterioration n = 14</i>					
Active lupus nephritis	12*	Extrarenal activity and positive serology	Performed in 10: "active" in all (9 biopsies, 1 necropsy)	Aggressive‡	6 deaths within 1 month; 1 death at 3 months
Unknown lupus activity	1	No extrarenal activity; serology not available	—	Aggressive	Death in 2 days
Acute renal failure	1	No extrarenal activity, negative serology	Acute tubular necrosis at necropsy	Not aggressive	Death in 2 days
<i>Chronic deterioration n = 10</i>					
Inactive lupus nephritis	9†	No extrarenal activity, positive serology	Performed in 7: chronic changes in all	Not aggressive	1 death within 1 week; 1 death within 1 month; 1 death at 2.5 months; 1 death after 5 years
Inactive lupus nephritis and possible interstitial nephritis	1	No extrarenal activity, negative serology	Chronic changes and interstitial infiltrate	Aggressive	Alive

*Early deterioration in 8, late deterioration in 4.

†Late deterioration in all.

‡High dose oral (60 mg 24 h) or intravenous (1 g daily for three days) methylprednisolone.

Timing of entry into terminal renal failure or death in patients with lupus nephritis. Vertical columns show distribution in time of renal and non-renal causes of death. Continuous line shows actuarially calculated proportion of 138 patients surviving at risk at various times of follow up.

Patients entering terminal renal failure with active lupus and a rapid decline in renal function therefore pose a difficult problem in terms of management, which we have discussed elsewhere.²² The added effects of immunosuppression, rapidly advancing uraemia, and active disease^{25, 26} predispose to infection but, on the other hand, potent treatment is required to suppress extrarenal manifestations and also to halt and possibly reverse the renal lesions.^{27, 28} Despite an aggressive therapeutic approach, most of our patients in this "acute" group died from active systemic lupus erythematosus. Possible explanations are that they were still undertreated, that aggressive treatment was started too late, or that they represented a particularly severe form of the disease which is resistant to available treatments. Those patients with slowly progressive renal dysfunction and inactive disease are predictably easier to manage, as it is possible to decrease immunosuppression to minimal levels sufficient to control extrarenal manifestations and start preparations for replacement therapy once renal failure is moderately advanced, as was suggested by Coplon *et al* and Friedman several years ago.^{29, 30} In our series four out of 10 patients in this group died, one of the deaths occurring five years after transplantation.

Reports on survival of patients with lupus undergoing renal replacement therapy are conflicting. Some workers note high mortality rates—for example, Kimberly *et al*¹⁹ reported 15 deaths in 39 patients undergoing dialysis, Rosner *et al*¹⁶ 30 deaths in 57 patients in a large multicentre study, and the 1982 combined report of the European Dialysis and Transplant Association Registration

Committee²⁰ a first year survival rate of only 76.4% in 815 patients undergoing first dialysis not followed by transplantation and a high mortality rate in the early months after transplantation. Others have had more encouraging results,^{17, 31-35} and recently Coplon *et al* found the long term clinical course after end stage renal failure in 28 patients to be comparable to that of patients undergoing replacement therapy from other diseases.¹⁸ These discrepancies may result from the exclusion of the more acute group of patients in those series having better results, which mainly include patients with stable, long term renal failure, as recognised by Coplon *et al*¹⁸ and discussed by us.²² We find that this "acute" group forms a considerable proportion of patients with lupus nephritis reaching end stage renal failure. Our results resemble those of Kimberly *et al*, who found that eight of their 15 deaths occurred shortly after the start of dialysis and were due to persistence of the increase in disease activity that led to end stage renal failure.¹⁹ In the series of Rosner *et al* systemic lupus erythematosus was active at the time of death in 21 of 30 deaths, which occurred significantly sooner than in those patients dying with inactive lupus. It is not clear in their study, however, whether the patients dying with active lupus had reached end stage renal failure as the result of active nephritis.

Urowitz *et al* first drew attention to the emergence of what they called a bimodal mortality pattern in systemic lupus erythematosus⁹—namely, early deaths with active lupus, mainly due to nephritis and infection; and late deaths associated with inactive lupus, principally due to myocardial infarction. This was confirmed by Karsh *et al* in their study of mortality in lupus nephritis,¹³ which suggested an early mortality from lupus and sepsis, a late mortality from vascular disease, and a constant death rate from renal failure. This pattern has been interpreted as the result of control of acute early manifestations of the disease in some patients, who thus enter a chronic phase, with eventual losses from causes not classically related to lupus and not affected (or even made worse) by treatment.^{3, 36} In our series the analysis was slightly different and this pattern not so clear; although active lupus and, to a less extent, infection were appreciably more common as causes of early deaths, and vascular events a cause of late deaths, there were many late deaths due to active lupus (table V). This would fit with a model of disease activity similar to that suggested by Urowitz *et al*⁹ and Albert³⁶ but taking into account the known relapsing course of the disease. Renal deaths were commonly a late event, while death from extrarenal causes (34% of the total) fell predominantly in the early death group.

Fries *et al* found that most patients went through a phase of lupus nephritis characterised by inactive systemic and renal disease but a slow decline in renal function.³⁷ In our study this pattern was the exception rather than the rule; only 12 patients out of a total of 26 had such a course and 12 reached end stage renal failure as a result of active lupus nephritis, commonly as an early event in their disease (eight patients) but also late in its course (four).

Finally, accelerated atherosclerosis is now a well recognised complication of systemic lupus erythematosus³⁸⁻⁴³ but its relative importance and causes are matters of controversy. Recently in a

large multicentre study, Rosner *et al* found vascular events to be an infrequent cause of death¹⁶ (only six patients died from myocardial infarction and another six from cerebrovascular accident out of a total of 22 deaths); but in other series myocardial infarction was reportedly much more commonly responsible for the death of patients suffering from systemic lupus erythematosus.^{9 13 38-42} We found that vascular events were a relatively uncommon but none the less important cause of death (7 out of 41 patients). The finding of six young women patients (all under 40) with severe ischaemic heart disease is striking and raises the possibility that obvious or unidentified atherogenic factors may be responsible for the particularly advanced disease in a subgroup of patients.

Vascular disease in systemic lupus erythematosus has been attributed variously to corticosteroids,⁴¹ hypertension, and the persistence of nephrotic hyperlipidaemia,⁴³ chronic renal failure, or the disease itself. The most interesting possibility, however, is that in some way the immunological events of systemic lupus erythematosus—and in particular the abundant circulating immune complexes—interact with other risk factors for cardiovascular disease which may be present to increase the risk of disease events to high levels.^{8 42} The presence of circulating immune complexes is known to potentiate the effect of a high lipid diet in rabbits⁴⁴ and baboons⁴⁵ and the restriction of fat in the diet⁴⁶ or the feeding of eicosapentaenoic acid⁴⁷ to protect NZB/W mice from vascular lesions, in the latter case also prolonging life by ameliorating the renal disease. By contrast, feeding a high fat diet accelerates the glomerular disease.⁴⁶⁻⁴⁸ In these mice as well as those of the MRL/1 and B xSB strains myocardial infarction is a common event, affecting 25-30% of mice.⁴⁹ In the important study of Haider and Roberts the degree of post-mortem narrowing of the coronary arteries in patients dying of systemic lupus erythematosus under the age of 40 was compared with age and sex matched controls.⁴² Advanced lesions were present in half the patients, the remainder showing narrowing comparable to that in the control group. In these two subgroups those with coronary narrowing showed higher serum cholesterol concentrations, higher blood pressure, and non-coronary heart lesions such as pericarditis and valve lesions, but the corticosteroid dosage was the same.

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Addendum

After this paper was written a further patient, a girl aged only 12, died of a myocardial infarct proved at necropsy just after starting regular dialysis. She had had lupus for only 18 months and the condition appeared to be an acute vasculitis rather than degenerative disease. Ishikawa *et al* also described myocardial infarction in a child with lupus, from diffuse atherosclerosis only two years from onset of lupus.⁵⁰

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WORDS DISORIENTATED, in a clinical context, means mentally confused; being grossly mistaken regarding one's place in the environment or, by extension, in time. Disorientation may also rarely occur in healthy people during difficult flying conditions.¹ Etymologically, disorientated means not knowing in which direction east lies; *L. orire, orientem*, to rise; hence the region of the globe beyond that point on the horizon at which the sun rises; the orient, the East (as viewed from Europe). But why not the West? Why should a confused person not be described as "disocciatedentated" (not knowing in which direction west lies)?

"Oriental" and "occidental" date from the fourteenth century. Major European travel during the preceding century was eastward (the Crusades, Marco Polo), and thoughts on far off lands were turned in that direction. Perhaps the clue lies there. Homologues of "disorientated" exist in all Romance languages (*F. desorienté, Sp. desorientado*)—with one curious exception, Portuguese, in which language the equivalent term is "des-norteadado." Linguistically, the Portuguese, when confused, do not know in which direction north lies. This probably stems from the days of the great Portuguese navigators of the early sixteenth century, notably Vasco da Gama and Magellan. At sea by night they would have depended for direction finding on Polaris the north star.—B J FREEDMAN.

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