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Skeletal Complications in the Renal Transplant Recipient

A clinical study

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II Elmstedt, E., Svahn, T. (1980)
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IV Elmstedt, E. (1980)
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V Elmstedt, E. (1980)
The incidence of skeletal complications in renal graft recipients:
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CONTENTS

INTRODUCTION

The relationship between chronic renal disease and skeletal alterations has been recognized since the end of the nineteenth century,[69] but it was not until about 1920 that the nature of the disease was elucidated. At that time several workers reported delayed skeletal development and rachitic alterations in children with renal damage[8,17,84] and in 1937 Albright and associates demonstrated skeletal lesions similar to those in hyperparathyroidism in patients suffering from chronic renal failure.[3] That these changes included osteitis fibrosa cystica, besides osteomalacia, was later confirmed by histological observations.[34,41] Renal osteodystrophy has been adopted as the accepted designation for the skeletal alterations accompanying renal failure,[67] which are now considered to include also osteosclerosis, osteoporosis and metastatic calcification.[71] The most important clinical feature in the adult is the occurrence of spontaneous fractures, and in the child disturbances in growth and development, rachitic lesions and epiphyseolysis.[25] The pathogenesis, which is complex, includes impaired metabolism of vitamin D, calcium, phosphorus and parathyroid hormone. The loss of renal tissue inhibits the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, with consequent depressed intestinal absorption of calcium and defective bone mineralization.[4,11,97] Increasing renal failure is accompanied also by hyperphosphataemia, which lowers the serum calcium concentration and thus stimulates the development of secondary hyperparathyroidism.[12]

This renal osteodystrophy is almost invariably present in terminal renal failure.[15,78] The lengthening of the patient's life achieved through haemodialysis often results in an increase in the symptomatic renal osteodystrophy.[15,33,58] Renal transplantation has created the theoretical conditions for obtaining a complete cure of renal osteodystrophy through restoration of vitamin D metabolism[51] and the calcium-phosphorus balance,[94] with consequent normalization of the parathyroid gland function.[38,48,85,107] The results of histomorphometric studies have confirmed the regression of osteomalacia and osteitis fibrosa changes after transplantation.[15,16,19,33] On the other hand, there is no improvement in the osteopenia, and bone loss continues, as has been most clearly demonstrated by X-ray spectrophotometry[26] and photon absorptiometry.[2,70,75] It is then perhaps hardly surprising to find that the incidence of spontaneous fractures in uremics is higher after than before the transplant operation.[43,65] Because avascular bone necrosis is also a common complication of renal transplantation, skeletal damage

presents a serious problem in such patients and is sometimes the only obstacle to rehabilitation. Avascular bone necrosis was first reported by Starzl and associates in 2 renal transplant patients in 1964[98] and the reported incidences vary widely – from 3 to 41 per cent. The series are often small, and the fact that in some cases no minimum graft survival time has been stipulated complicates the calculation of incidence figures (Table 1). Moreover, the follow-up times observed vary widely. As regards the occurrence of spontaneous fractures after renal transplantation the accounts are few and here, too, the incidence data are controversial (Table 2).

The information on morbidity and treatment methods is strongly divergent. It is agreed that avascular necrosis of the femoral head is the main clinical problem, but whereas some centres have operated on about 20 per cent of these patients,[53] at other units the figure is nearer 80 per cent.[104] Total hip replacement is now the form of surgical treatment in most common use,[45,92] but some groups report excellent results obtained with cup arthroplasty and femoral head prostheses.[32] There are also advocates for less radical operations such as osteotomy,[24] drilling[64] and cortical bone graft.[72]

The pathogenesis of the skeletal complications of transplantation is still a matter of controversy. Some workers have found that among patients with avascular bone necrosis the total intake of prednisone was higher, the numbers of rejection periods and retransplantations were greater[49] and the dialysis times were longer.[5] Others have reported elevated incidences of hyperparathyroidism[20] and hypophosphataemia[14] in avascular necrosis patients, but in many studies no such differences have been detected.[21,53,65,101,103] Spontaneous fracture has generally been considered to be a side effect of immunosuppressive therapy but no association has been found between the individual dose of steroids and the bone loss.[2,66,75,82]

AIMS OF THE INVESTIGATION

This investigation was undertaken with a view to resolving some of these inconsistencies and examining further the serious problems presented by these skeletal complications and disclosed in a preliminary study (Study I).

More specifically the main purposes of the research were

1. To examine the occurrence of skeletal complications in a large series of renal transplant patients with a long survival time, with particular emphasis on the incidence of the various complications, their clinical features and the forms of treatment.

TABLE 1 Incidence of avascular bone necrosis in the renal graft recipients

Investigator		Ref no.	Shortest graft survival, months	No. of patients	Avascular bone necrosis No.	Per cent
Cruess	1968	21	6	27	10	*37*
Eremin	1969	31	2	34	6	*18*
Nelson	1971	77	-	242	15	*6*
Bell	1972	10	6	27	4	*15*
Briggs	1972	14	3	130	11	*8*
Elmore	1972	30	-	198	11	*5*
Kinnaert	1972	59	-	96	3	*3*
Troch	1972	103	3	90	13	*15*
Woods	1972	106	-	120	6	*5*
Murray	1973	76	-	330	46	*14*
Gaucher	1974	40	8	28	7	*25*
Harris	1974	50	6	48	15	*31*
Arfi	1975	5	12	160	29	*18*
Pierides	1975	86	12	78	11	*14*
Ølgaard	1975	83	-	197	15	*8*
Bewick	1976	11	-	378	13	*3*
Chatterjee	1976	20	12	68	8	*12*
Hawking	1976	52	9	44	18	*41*
Levine	1977	65	6	100	16	*16*
Nielsen	1977	79	6	195	22	*11*
Ibels	1978	53	4	194	40	*21*
Potter	1978	87	-	100	11	*11*
Rosekrans	1978	91	6	85	21	*25*
Susan	1978	101	-	388	19	*5*
Uittenbogart	1978	104	-	171	11	*6*
Stern	1979	99	24	36	9	*25*

2. To identify any factors bearing on the occurrence of skeletal complications after renal transplantation.
3. To reduce the risk of skeletal complications by eliminating as far as possible any such factors.

TABLE 2 Incidence of spontaneous fracture in the renal graft recipients

Investigator		Ref. no.	Shortest graft survival, months	No. of patients	Fracture	
					No.	Per cent
Hall	1969	46	-	120	4	*3*
Evarts	1971	32	-	203	4	*2*
Griffiths	1974	43	-	225	30	*13*
Harris	1974	50	6	48	6	*13*
Levine	1977	65	6	100	14	*14*
Nielsen	1979	82	6	195	18	*9*

MATERIAL AND METHODS

PATIENTS

In Stockholm between 1964 and 1976 a total of 392 renal transplantations were performed in 307 patients. The 204 patients whose grafts were still functioning after 12 months constitute the main material for these studies. They were followed for between 12 and 165 months (median 46 months). The patients - 117 males and 87 females - were aged from 6 to 66 years. The most common underlying renal diseases were chronic glomerulonephritis, chronic pyelonephritis and polycystic kidney disease (Table 3). Parathyroidectomy was performed for hyperparathyroidism in 24 patients, in 18 of them before, and in 6 after, the transplant operation. The indication for surgery in 22 cases was secondary, and in 2 cases tertiary, hyperparathyroidism. Two grafts had been received by 31 patients and 3 by 1 patient. Living related donors furnished 64 of the kidneys, while 140 came from cadavers.

In November 1977 the pharmacotherapy given to such patients at this hospital was modified. The 71 patients undergoing 73 transplantations between November 1977 and May 1979 were therefore examined as a separate group. Of the patients receiving their first renal graft the 36 where this was still functioning after 12 months constituted the series for Study V (Table 4). Twenty-two of them were men and 14 were women. Two of the patients received 2 graft kidneys during this period. In 16 cases the donors were living relatives while in 20 cadaveric kidneys were used. The patients ranged in age from 12 to 68 years. The follow-up time was from 12 to 30 months. None of the patients had undergone parathyroidectomy.

All patients have been attended by the author since 1974.

TABLE 3 Frequencies of various clinical factors among the patients with avascular bone necrosis and spontaneous fracture

	Total no.of patients	Avascular bone necrosis		Spontaneous fracture	
		No.	Per cent	No.	Per cent
All patients	204	11	*22*	53	*26*
< 30 years	53	4	*8*	7	*13*
30-45	72	4	*6*	20	*28*
46-60	68	11	*16*	23	*34*
> 60	11	3	*27*	3	*22*
LD	64	5	*8*	13	*20*
CD	140	17	*12*	40	*29*
Males	117	14	*11*	30	*26*
Females	87	8	*9*	23	*26*
Pre-op.parathyroidectomy	18	4	*22*	7	*39*
No " -	186	18	*10*	46	*25*
Transplantations:					
One	172	19	*11*	42	*24*
Two or more	32	3	*9*	11	*32*
Chronic glomerulonephritis	81	9	*11*	20	*25*
Chronic pyelonephritis	41	6	*15*	11	*27*
Polycystic kidney disease	25	1	*4*	10	*40*
Chronic nephritis	20	4	*20*	4	*20*
Diabetic nephropathy	9	0	*0*	3	*33*
Interstitial nephropathy	7	1	*14*	1	*14*
Other kidney diseases	21	1	*5*	4	*19*

SURGICAL TECHNIQUE

The graft artery was usually anastomised end-to-end to the hypogastric artery, except in a few instances when an end-to-side anastomosis to the external iliac artery was used. Venous drainage was effected by an end-to-side anastomosis to the external iliac vein. The ureter was implanted in the bladder and the kidney was placed extraperitoneally in the pelvis.

TABLE 4 Clinical series reported in Studies I - V

	Period	No.of trans-plant.	No. of patients	Graft survival, > 12 months	M/F	LD/CD	Age years	>IT/IT[a]	Follow-up, months
Study									
I	1964-73	220	199	99	62/37	35/64	6-66	12/77	12-129
II	1964-76	392	307	204	117/87	64/140	6-66	32/172	12-165
III-IV	1972-76	261	230	144	78/66	45/99	6-66	25/119	12-83
V	1977-79	73	71	36	22/14	16/20	12-68	2/34	12-30

[a] Number of patients receiving more than 1 renal graft/number receiving 1 graft

IMMUNOSUPPRESSION

In all cases azathioprine and prednisone were given orally as a prophylactic immunosuppressive measure, the former usually in doses of 2 - 3 mg/kg/d, but less if leukopenia had developed. Prior to 1977 the initial dose of prednisone had usually been 200 mg/d, with a smaller amount for children and adults of very small stature; this dose was gradually lowered to 20 - 40 mg/d at 1 month after the transplant operation, and then at a lower rate down to a maintenance dose of 10 - 20 mg/d at 1 year. In a few of the earliest patients to be treated the initial dose was as high as 400 mg/d, and at 1 month 40 - 70 mg/d. From 1970 onwards 1 g of alpha-methyl prednisolone was given intravenously on each of the first 3 days after the transplant operation. In November 1977 the initial oral dose of prednisone was reduced to 100 - 120 mg/d and the initial 1 g doses were withdrawn.

Most of the patients also received anti-lymphocyte globulin as a prophylactic immunosuppressive measure. Between 1966 and 1971 various preparations and dose schedules were used, but from September 1971 onwards this drug was given as a commercially available standardized product (Behring).[44] The dose of 15 - 30 mg/kg was given intravenously on the first 21 days after the transplant operation. Drainage of lymph through a duct fistula was performed as an adjunctive immunosuppressive measure in 52 of the patients.[39] Where possible the fistula was kept open for 1 - 2 months.

In the event of an acute rejection episode the daily oral dose of prednisone was increased to 200 mg, and then gradually reduced again to the maintenance level. During the period 1964 - 71 this treatment was combined

with Actinomycin C given intravenously - 1 g daily on 3 consecutive days. The treatment for most of the rejection episodes included local irradiation of the graft kidney - 150 R on 3 consecutive days. From 1970 the treatment schedule was supplemented with the intravenous administration of alpha-methyl prednisolone - 1 g on 3 consecutive days. In some cases where chronic rejection was diagnosed the oral maintenance dose of steroids was increased by 5 - 20 mg. From November 1977 the rejection treatment consisted in the administration of 1 g of alpha methyl prednisolone for 3 - 5 days, but without raising the oral dose of prednisone.

To avoid gastrointestinal side effects of steroids large doses of antacids were given, expecially during the first month after the transplant operation; phosphate-binding compounds such as aluminium hydroxide were generally used (10 - 15 ml 6 - 10 times a day) up until 1977, when a change was made to aluminium phosphate, which is not phosphate-binding.

DIAGNOSTIC AND FOLLOW-UP PROCEDURES

The diagnosis of skeletal complications was based on hospital records, regular patient interviews, clinical examinations and radiological findings. In the event of symptoms at any one site - the shoulders, hips or knees - radiographic and scintigraphic examinations of all these joints were made (5 mCi ^{99m}Tc pyrophosphate).[9,28] Repeated clinical examinations and serial scintigraphic examinations of these joints were then carried out in at intervals of 6 months. A quantitative measurement of the uptake was performed by means of a computer-aided gamma camera concurrently with a morphological analysis of the analogous image (Fig. 1).

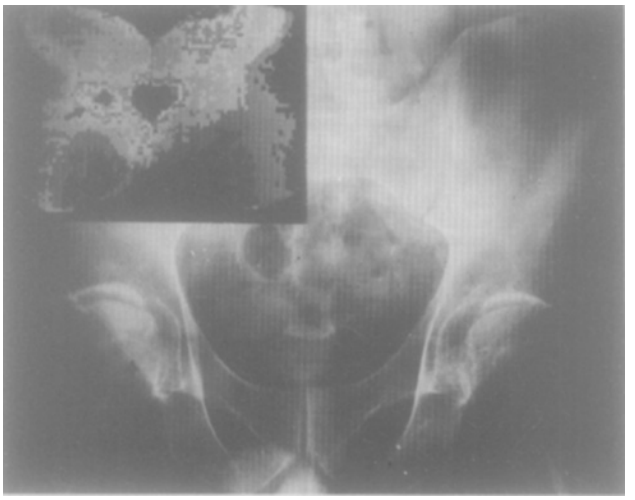

Fig. 1

The patients receiving treatment were followed up clinically and radiographically every 6 - 12 weeks. The sex, age, renal disease, origin of the graft and the HLA match of the graft and any parathyroidectomy were recorded, as were the dialysis times, duration of postoperative care, number of rejection episodes and duration of graft function. The serum concentrations of creatinine, calcium, phosphorus and alanine-amino-transferase (ALAT) were measured by routine laboratory techniques before, and at regular intervals after, the transplant operation (1 week, 1, 2, 3, 6 and 12 months). The patient's weight was recorded on the same occasions.

The steroid and azathioprine intakes were recorded continuously. The total oral dose of azathioprine and the daily dose related to body weight and body surface area were calculated for each patient for periods of 1, 2, 3, 6 and 12 months after the transplant operation. The same calculations were performed for the oral dose of prednisone and for the total dose of steroids - that is, oral prednisone and intravenous methyl prednisolone.

STATISTICAL METHODS

The results are presented as the arithmetic mean and the standard deviation or the median and the largest and smallest values. Values that were not normally distributed were log normally distributed and then logarithmized before being subjected to statistical analysis. For the comparison of individual means in two groups Student's t test was used (Study V). Differences between the incidences of skeletal complications for various groups were tested by chi-square analysis (Studies II and V). In the studies of factors possibly having a bearing on the occurrence of skeletal complications discriminant analysis was used (Studies III and IV). The statistical computations were performed at Systemgruppen, Karolinska Institute, using the Statpac programme.

RESULTS

INCIDENCE (Table 3)

Spontaneous fractures were sustained by 6 of the 204 patients (3 per cent) before transplantation and by 53 (26 per cent) afterwards. They were aged from 10 to 63 years, most of them being above 45 years ($P < 0.05$) (Study II).

Avascular bone necrosis developed in 22 patients (11 per cent); they were between 21 and 61 years of age, most of them again being over 45 ($P < 0.01$) (Study II).

The incidence of skeletal complications was similar for the male and female patients. There was no significant difference between the recipients of graft kidneys from relatives and of those from diseased persons (Study II).

The number of HLA incompatibilities among the cadaveric donors was evidently of no importance for the development of skeletal complications, nor was it of significance whether the living donor grafts were HLA identical or not (Studies III and IV). Neither the number of spontaneous fractures nor the occurrence of avascular bone necrosis was dependent on whether parathyroidectomy had been performed, or on whether it had been carried out before or after the transplant operation (Study II). The occurrence of skeletal complications was not more common among the patients that had had more than one renal transplantation, nor was there an association with the type of renal disease (Study II).

CLINICAL FEATURES

Avascular bone necrosis (Study II): The period elapsing between the transplant operation and the onset of signs and symptoms of this complication ranged from 5 to 46 months (mean 15); in 11 of the 22 patients it was less than 12 months. In 14 patients the lesion was confined to a single bone, while in the rest of the patients between 2 and 6 sites were involved (Table 5). Altogether 40 bones were affected, 35 of them weight-bearing. The most common sites were the femoral heads, both of which were affected in 6 patients; other sites were the femoral condyles, humeral head, proximal tibia, talus and the scaphoid and navicular bones (Fig. 2). Fractures occurred in 8 patients with avascular bone necrosis.

Spontaneous fracture (Study II): The interval between the transplant operation and the first fracture ranged from 1 to 58 months (median 15). The 53 patients sustained a total of 109 fractures. A single fracture was recorded in 29 patients, while one recipient had as many as 7 fractures (right femoral neck, all 4 ischiopubic rami, right calcaneus and fibula) (Table 5). The axial skeleton and trunk were the sites of 69 per cent of the

fractures, the pubic bone being the most commonly affected (39 of 109 or 33 per cent). Non-weight-bearing structures were involved in 7 per cent (invariably the arms; and in one half of them the radii) (Fig. 2).

TABLE 5 Frequencies of various numbers of lesions in the patients with skeletal complications

	Patients with avascular bone necrosis		Patients with spontaneous fracture	
	No.	Per cent	No.	Per cent
No. of lesions				
1	14	*64*	29	*55*
2	3	*14*	7	*13*
3	2	*9*	8	*15*
4	2	*9*	5	*9*
5			3	*6*
6	1	*5*		
7			1	*2*

RADIOLOGICAL FINDINGS

The radiographic changes in avascular bone necrosis usually did not appear until a few months after the clinical symptoms had become manifest. In the hip and shoulder joints the lesion initially consisted of a thin circumscribed, subchondral zone of demineralization (Fig. 3). At a more advanced stage the articular surface was deformed and irregular sclerosis of the underlying bone was seen. In some instances, especially where the non-weight-bearing joints were affected, no collapse occurred.

All patients with manifest osteonecrosis of the hips were also examined in the erect position. In none was there reduction of the articular cartilage (Study I).

POTENTIAL RISK FACTORS

Calcium-phosphorus balance (Table 6): On no occasion during the first year after transplantation did the serum calcium or serum phosphorus concentrations for the groups with and without spontaneous fractures differ significantly (Study IV). According to the discriminant analysis the serum phosphorus concentration 2 months after the transplant operation was significantly lower for the patients developing avascular bone necrosis than for

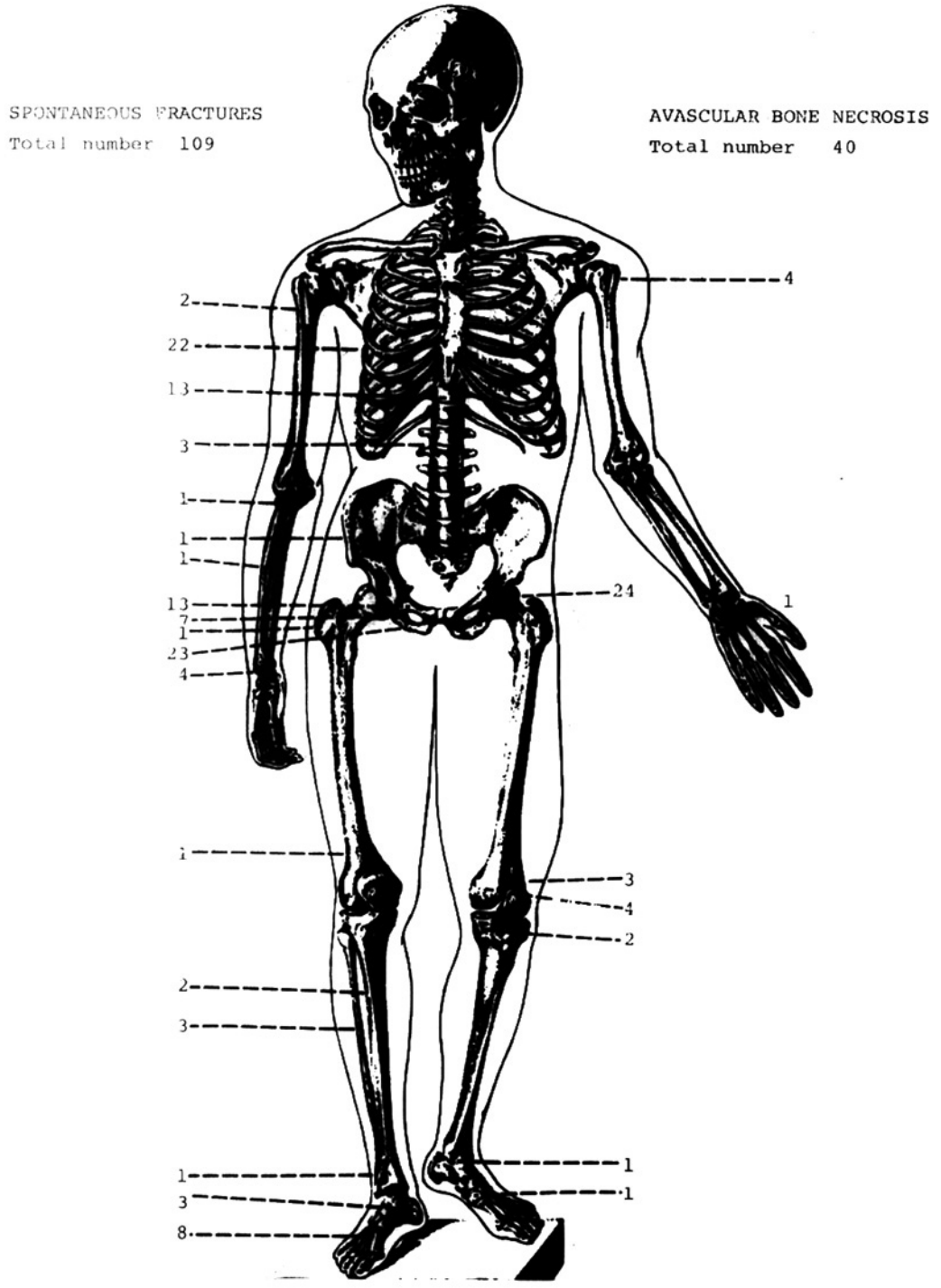

Fig. 2 Location of skeletal complications in 204 recipients whose grafts were still functioning after 12 months.

TABLE 6 Calcium and phosphorus values recorded in renal transplant recipients with and without skeletal complications

	Avascular bone necrosis				Spontaneous fracture			
	Present		Absent		Present		Absent	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of patients	19		125		38		106	
Serum calcium, mmol/l								
1 week after transplantation	2.108	0.232	2.191	0.209	2.179	0.244	2.181	0.202
1 month " -	2.231	0.285	2.312	0.211	2.329	0.249	2.292	0.213
2 months " -	2.425	0.268	2.388	0.208	2.419	0.241	2.383	0.207
3 " -	2.467	0.402	2.402	0.215	2.418	0.215	2.408	0.258
6 " -	2.412	0.197	2.421	0.200	2.406	0.232	2.425	0.186
12 " -	2.425	0.188	2.390	0.204	2.422	0.216	2.385	0.197
Serum phosphorus, mmol/l								
1 week after transplantation	0.845	0.547	0.873	0.521	0.834	0.520	0.883	0.525
1 month " -	0.702	0.305	0.824	0.370	0.746	0.313	0.830	0.379
2 months " -	0.682	0.289	0.891	0.290	0.868	0.313	0.862	0.294
3 " -	0.946	0.420	0.889	0.333	0.888	0.297	0.899	0.361
6 " -	0.994	0.237	1.012	0.261	1.012	0.243	1.009	0.264
12 " -	1.103	0.358	1.010	0.219	0.996	0.210	1.032	0.253

the group without this complication ($P < 0.01$) (Study III). When the discriminant function was based on the serum phosphorus levels 2 months after the transplant operation it was found that 12 of the 19 patients developing osteonecrosis could be expected to be affected by this condition (Table 7).

TABLE 7 Classification of the renal graft recipients with respect to presence or absence of avascular bone necrosis. The discriminant function was formed from the variable serum phosphorus concentration 2 months after the transplant operation

		Avascular bone necrosis	
		Present	Absent
Classification			
With avascular bone necrosis		12	38
Without " -		7	87
Correctly classified	*Per cent*	*63.2*	*69.6*

Hepatic and renal function (Table 8): Between the groups with and without skeletal complications there was no significant difference in hepatic function during the first year after the operation insofar as this was reflected in the alanine-amino-transferase (ALAT) levels (Studies III and IV).

Nor were there any significant differences between these groups as regards the serum creatinine levels after transplantation. The importance of the normalization of renal function for the occurrence of skeletal complications was examined on the basis of the depression of the serum creatinine level 1 week after transplantation. Stepwise discriminant analysis showed then that the incidence of osteonecrosis increased inversely as the rate of normalization (Tables 7 and 9) (Study III).

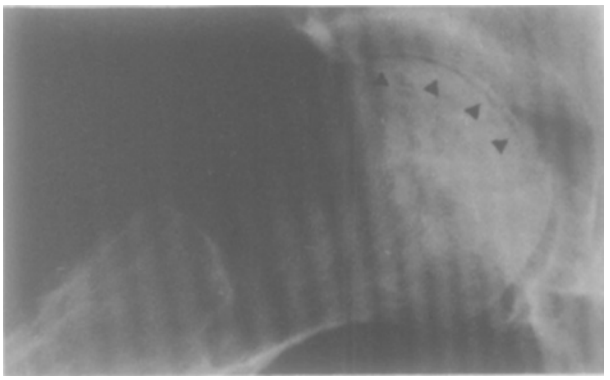

Fig. 3

TABLE 8 Serum creatinine and alanine-amino-transferase values in the renal graft recipients with and without skeletal complications

	Avascular bone necrosis						Spontaneous fracture					
	Present			Absent			Present			Absent		
	Median	Min.	Max.	Median	Min.	Max.	Median	Min.	Max.	Median	Min.	Max.
Number of patients	19			125			38			106		
Serum creatinine mmol/l												
1 week before transplantation	831	150	1238	807	308	1591	813	300	1530	805	150	1591
1 " after "	141	64	1000	130	40	1176	130	53	943	131	40	1176
1 month " -	106	60	245	106	48	320	106	53	239	108	48	320
2 months	106	60	230	110	50	440	109	53	213	114	50	440
3 " -	119	50	241	112	47	296	110	53	241	114	47	296
6 "	127	60	210	110	60	360	117	60	256	114	60	360
12 " -							120	60	280	116	61	330
Decrease 1 week before — 1 week after	480	-810	1114	600	530	1445						
Alanine-amino-transferase (S-ALAT)												
1 week after transplantation	0.430	0.200	3.510	0.450	0.170	3.970	0.455	0.170	3.970	0.450	0.170	3.820
1 month " -	0.430	0.170	1.200	0.420	0.100	3.000	0.400	0.180	3.000	0.455	0.100	2.900
2 months " -	0.450	0.200	2.170	0.450	0.170	3.510	0.390	0.170	2.890	0.470	0.170	3.510
3 " -	0.520	0.290	4.110	0.450	0.170	16.700	0.410	0.170	4.110	0.500	0.170	16.700
6 " -	0.720	0.220	4.650	0.490	0.080	14.700	0.475	0.080	1.490	0.540	0.130	14.700
12 " -	0.740	0.220	4.290	0.470	0.170	12.160	0.540	0.180	2.430	0.480	0.170	12.160

TABLE 9 Classification of the renal graft recipients with respect to the presence or absence of avascular bone necrosis. The discriminant function was formed from the variables serum phosphorus concentration 2 months after the transplant operation, age and decrease in serum creatinine level at 1 week.

		Avascular bone necrosis	
		Present	Absent
Classification			
With avascular bone necrosis		15	35
Without " -		4	90
Correctly classified	*Per cent*	*78.9*	*72*

Clinical factors (Studies III and IV): The differences in age of the patients with and without skeletal complications were not statistically significant (Table 10), but the stepwise discriminant analysis showed that the incidence of avascular bone necrosis increased with age. When the formation of the discriminant function was based not only on the serum phosphorus level at 2 months but also on age and normalization of renal function the accuracy of the prediction was improved to 15 out of the 19 affected patients (Table 9).

There was no difference between the groups with and without skeletal complications as regards the dialysis time or the duration of postoperative care or of graft function. Nor was there any significant difference in the number of rejections. The groups with and without skeletal complications did not differ significantly in weight (Table 10), or as regards the absolute or relative increase in weight during any period in the course of the first year after the transplantation.

Immunosuppression (Studies III and IV): For none of the periods during the first 12 months after the transplantation was there any difference between the patient groups with and without skeletal complications as regards the total intake of azathioprine or the mean 24-hour intake in relation to weight or to body surface area (Table 11). The amount of steroids administered during the first 3 months after the transplant operation was smaller for the group with than for that without fracture ($P < 0.01$). This was the case for the oral dose of prednisone, the total dose of steroids and the mean daily amounts of these drugs in relation to weight and body surface area.

TABLE 10 Clinical findings in renal graft recipients that developed skeletal complications and in those that did not

	Avascular bone necrosis				Spontaneous fracture			
	Present		Absent		Present		Absent	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Number of patients	19		125		38		106	
Living donor graft	4/19	*21*	41/125	*33*	11	*29*	34	*32*
HLA identical	0/4	*0*	11/41	*27*	3/11	*27*	8/34	*24*
Not HLA indentical	4/4	*100*	30/41	*73*	8/11	*73*	26/34	*76*
Cadaveric donor graft	15/19	*79*	84/125	*67*	27	*71*	72	*68*
0-2 HLA incompatibilities	11/15	*73*	61/84	*73*	23/27	*85*	49/72	*68*
3 or 4 HLA incompatibilities	4/15	*27*	23/84	*27*	4/27	*15*	23/72	*32*
Duration of dialysis, days [a]	Md 150 min:0 max:1965		Md 105 min:0 max:2880		Md 150 min:0 max 2880		Md 120 Min:0 max 2110	
Age, years Mean ± S.D.	46.4	11.1	39.9	14.2	43.6	13	39.7	14.3
Duration of postoperative care, days " -	31.6	8.9	32.9	1.6	31.8	15.9	33.0	14.8
Duration of graft function, months " -	48.8	17.8	45.4	19.5	49.0	17.8	44.8	19.7
Number of rejections " -	1.6	1.5	1.4	1.4	1.6	1.7	1.3	1.3
Body weight, kg								
1 month after transplantation " -	60.79	9.36	58.24	12.83	57.31	12.15	59.04	12.55
2 months " - " -	62.17	10.36	59.92	12.57	58.73	11.64	60.74	12.52
3 " - " -	64.12	10.47	61.18	12.21	60.53	11.51	61.94	12.20
6 " - " -	67.33	10.71	64.16	12.53	63.56	11.85	64.94	12.51
12 " - "-	70.22	11.22	65.76	12.90	65.86	12.22	66.54	12.98

[a] Median, minimum and maximum used because the distribution was skew

TABLE 11 Azathioprine intake by the renal graft recipients with and without skeletal complications

		Avascular bone necrosis				Spontaneous fracture			
		Present		Absent		Present		Absent	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of patients		19		125		38		106	
Azathioprine									
Total intake, g	1 month	3.323	1.171	3.689	1.164	3.417	0.954	3.721	1.229
	2 months	6.197	2.619	6.894	2.472	6.135	2.019	7.041	2.610
	3	9.518	4.343	10.110	3.855	9.009	3.365	10.400	4.041
	6	21.200	8.741	20.200	7.877	18.980	7.914	20.810	7.973
	12	42.680	17.710	40.820	15.840	38.430	16.350	42.010	15.910
Mean daily intake	1 month	1.816	0.739	2.120	0.706	1.963	0.576	2.122	0.757
Related to body weight mg/d/kg	2 months	1.685	0.776	1.989	0.768	1.776	0.664	2.011	0.803
	3	1.723	0.848	1.953	0.810	1.738	0.722	1.989	0.840
	6	1.907	0.846	1.948	0.815	1.822	0.815	1.986	0.817
	12	1.944	0.823	1.957	0.793	1.836	0.817	1.998	0.785
Related to body surface area mg/d/m^2 BSA	1 month	64.11	24.13	73.39	22.49	67.77	18.52	73.74	24.09
	2 months	59.72	26.26	68.71	24.47	61.20	21.21	69.79	25.68
	3	61.05	28.89	67.29	25.81	59.91	23.39	68.81	26.87
	6	67.94	28.98	67.33	26.48	62.94	29.96	69.01	26.57
	12	69.58	28.63	67.87	26.11	63.64	27.37	69.69	25.93

TABLE 12 Intake of methyl prednisolone and oral and total steroids (oral prednisone plus intravenous methyl prednisolone) by the renal graft recipients with and without skeletal complications

		Avascular necrosis				Spontaneous fracture			
		Present		Absent		Present		Absent	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of patients		19		125		38		106	
Oral prednisone									
Total intake	1 month	3.334	1.321	3.083	0.818	2.858	0.714	3.208	0.942
g	2 months	5.532	1.961	4.843	1.709	4.267	1.380	5.173	1.815
	3	6.829	2.478	5.905	1.986	5.293	1.703	6.290	2.135
	6	9.238	2.619	8.311	2.358	7.873	2.193	8.634	2.455
	12	13.000	2.919	11.770	2.875	11.540	2.918	12.070	2.895
Mean daily intake	1 month	1.895	0.869	1.847	0.637	1.711	0.485	1.904	0.719
Related to body	2 months	1.520	0.581	1.406	0.565	1.242	0.405	1.485	0.603
weight	3	1.203	0.442	1.112	0.417	0.988	0.308	1.172	0.444
mg/d/kg	6	0.775	0.229	0.743	0.235	0.704	0.217	0.763	0.238
	12	0.526	0.144	0.514	0.152	0.498	0.153	0.522	0.150
Methyl prednisolone									
g	12	5.6	3.0	5.5	3.7	5.6	3.0	5.5	3.7
Total steroids									
Total intake	1 month	6.755	3.123	6.227	2.849	5.384	2.474	6.623	2.956
g	2 months	10.320	4.548	9.371	4.680	8.083	4.076	10.000	4.766
	3	11.930	4.939	10.680	4.947	9.345	4.319	11.380	5.065
	6	14.550	5.051	13.540	5.704	12.430	5.081	14.120	5.752
	12	18.630	5.630	17.210	6.232	16.490	5.707	17.730	6.304
Mean daily intake	1 month	3.670	1.811	3.594	1.797	3.056	1.397	3.800	1.882
Related to body	2 months	2.757	1.197	2.670	1.381	2.251	1.048	2.836	1.422
weight	3	2.115	0.865	2.023	0.976	1.729	0.734	2.144	1.010
mg/d/kg	6	1.293	0.460	1.280	0.548	1.161	0.465	1.325	0.554
	12	0.827	0.270	0.812	0.299	0.771	0.267	0.829	0.303
Related to body	1 month	130.5	63.78	124.3	58.89	106.1	47.92	132	61.74
surface area	2 months	98.68	43.7	92.67	45.3	78.78	36.87	98.73	46.62
$mg/d/m^2$ BSA	3	75.86	31.48	70.28	31.80	60.62	25.73	74.75	32.91
	6	46.23	16.26	44.55	18.00	40.47	15.58	46.32	18.27
	12	29.53	9.12	28.30	9.72	26.91	8.75	29.02	9.90

For no period during the first 12 months after the transplantation was there any difference in the intake of steroids by the patients with avascular bone necrosis and by those without this complication (Table 12).

TABLE 13 Intake of oral prednisone and total steroid (oral prednisone plus intravenous methyl prednisolone) during the year following the renal transplant operation, in the two series given the higher and lower doses of steroids

		Higher doses 1972 – 76		Lower doses 1977 – 79	
		Mean	SD	Mean	SD
Number of patients		144		36	
Oral prednisone					
Total intake, g	1 month	3.116	0.898	1.847	0.243
	2 months	4.934	1.753	3.025	0.282
	3	6.027	2.072	4.083	0.376
	6	8.433	2.405	6.528	0.657
	12	11.930	2.900	9.814	1.084
Mean daily intake Related to body weight mg/d/kg	1 month	1.853	0.669	1.031	0.343
	2 months	1.422	0.567	0.870	0.267
	3	1.124	0.420	0.782	0.239
	6	0.745	0.234	0.622	0.180
	12	0.515	0.151	0.463	0.131
Total steroids					
Total intake, g	1 month	6.296	2.881	4.417	3.289
	2 months	9.497	4.658	7.403	4.639
	3	10.850	4.947	9.461	5.575
	6	13.680	5.616	12.010	5.723
	12	17.400	6.157	15.357	5.902
Mean daily intake Related to body weight mg/d/kg	1 month	3.604	1.792	2.504	2,044
	2 months	2.681	1.355	2.111	1.376
	3	2.035	0.960	1.788	1.092
	6	1.281	0.536	1.134	0.578
	12	0.814	0.294	0.722	0.315
Related to body surface area, mg/d/m^2 BSA	1 month	125.200	59.360	86.975	66.152
	2 months	93.470	45.010	73.031	44.924
	3	71.020	31.710	62.158	36.218
	6	44.770	17.730	39.422	18.747
	12	28.460	9.630	25.161	9.848

MODIFICATION OF PHARMACOTHERAPY

Steroids (Study V): By lowering the oral dose of prednisone during the first 2 months after the transplant operation the steroid dose was reduced by about 40 per cent (Table 13). Though the reduction decreased with time it was still highly significant throughout the first 12 months after the operation ($P < 0.00001$). The total steroid dose - that is, oral prednisone and intravenous methyl prednisolone - was not decreased to the some extent as the oral dose. The first month after the operation the total steroid dose was about 70 per cent of the earlier value, but the difference decreased with time, and at 3 months the difference was just significant ($P < 0.05$) (Table 13).

Antacid agents (Study V): The group given phosphate-binding antacids and the group given non-phosphate-binding agents were compared as regards the serum phosphorus concentration recorded during the first 2 months after the transplant operation (Table 14). In respect of the change in the serum phosphorus level between 1 week and 2 months after the operation the patients receiving non-phosphate-binding agents showed a significantly higher level ($P < 0.005$).

TABLE 14 Serum phosphorus concentration in renal graft recipients given phosphate-binding and those given non-phosphate-binding antacids

	Serum phosphorus level, m mol/l			
	Phosphate-binding antacids		Non-phosphate-binding antacids	
	Mean	SD	Mean	SD
Number of patients	21		14	
Serum phosphorus level				
1 week after transplantation	0.962	0.581	0.593	0.377
1 month " -	0.766	0.583	0.693	0.325
2 months " -	0.676	0.369	0.843	0.279
Difference 1 w - 2 mo	-0.271	0.738	0.250	0.422

INCIDENCE OF SKELETAL COMPLICATIONS AFTER MODIFICATION OF PHARMACOTHERAPY

Of the 36 patients receiving a renal graft after November 1977, at which time a change in pharmacotherapy was introduced, 8 were found to have spontaneous fractures (22 per cent) against 22 of the 144 (19 per cent) receiving their graft between 1972 and 1976. Avascular bone necrosis was not present in any of the patients receiving their grafts after the modification of pharmacotherapy, but was found in 17 (12 per cent) of the patients in the earlier series ($P < 0.1$) (Study V) (Table 15).

TABLE 15 Skeletal complications in the renal graft recipients given the higher doses of steroids and the phosphate-binding antacids (1972 – 76) and lower doses of steroids and non-phosphate-binding antacids (1977 – 79).

	Higher steroid dose (1972 – 76)		Lower steroid dose (1977 – 79)	
	No.	%	No.	%
Number of patients	144		36	
Avascular bone necrosis	17	*12*	0	*0*
Spontaneous fracture	27	*19*	8	*22*

TREATMENT

Avascular bone necrosis (Study II): Conservative measures taken during periods of aggravation were adequate for patients with lesions at other sites than the hips. Where avascular necrosis of the femoral head had developed, with pain lasting more than 6 months, despite relief of load on the joints, surgery was considered to be indicated. Four hips in 3 patients fell into this class. In all of them total hip replacement with Charnley-Müller or CAD prostheses were performed. The recoveries were uneventful, and there was no sign of a change in renal function. For all 4 hips the end result was excellent, with good strength and mobility and no pain. The follow-up time ranged from 10 to 26 months.

Spontaneous fracture (Study II): Standard principles of treatment were applied. Neither pseudarthrosis nor delayed union was recorded in any of the patients, irrespective of whether the treatment was surgical or conservative.

GENERAL DISCUSSION

Unless otherwise indicated the results discussed below relate to patients receiving renal grafts.

INCIDENCE AND CLINICAL FEATURES OF AVASCULAR NECROSIS

The large variability of the reported incidences of this complication - ranging from 3 to 41 per cent (Table 1) - is due at least in part to differences between the patient materials; in some cases the figures are based on all the patients receiving renal grafts, while in others the patients shall have carried their grafts for a certain minimum time. Moreover, the follow-up times differ. If all the patients are taken into the series, including those that lost their graft early on and that thus received immunosuppressive therapy for only a short period, the incidence of osteonecrosis will be underestimated. The same applies if the follow-up time is short. We chose a minimum graft survival of 12 months as a criterion for inclusion of the patient in the study. In the only 3 other studies where the follow-up time was of this length the series were small; the incidences of avascular necrosis were 12, 14 and 18 per cent[20,86,5] against 11 per cent for our larger series.

Earlier studies, as well as our own, have furnished no evidence that the occurrence of avascular bone necrosis is correlated to sex, renal disease or origin of the graft.[30,76,79] Nor has any association between HLA compatibility and avascular bone necrosis been found in an earlier or the present investigation.[14,86]

The interval elapsing between the transplant operation and the onset of osteonecrosis in the present study was consistent with the times reported for other series, as were the characteristics of the lesion, such as a multifocal nature and a tendency for weight-bearing joints to be affected more than others.[11,53,65,86,103]

INCIDENCE AND CLINICAL FEATURES OF SPONTANEOUS FRACTURE

The incidences of spontaneous fracture in various series of renal graft patients range from 2 to 14 per cent (Table 2). In none of the earlier series did the follow-up time exceed 6 months. Since the median time for the occurrence of spontaneous fracture in this series was 15 months (Study II),

6 months is evidently too short a period for a realistic assessment of the incidence of the complication. Of the present large series of recipients whose grafts had functioned for more than 12 months as many as 26 per cent developed this complication.

A correlation between the decrease in bone mineral content (BMC) after transplantation and the development of fractures has been demonstrated.[2,80] The observation that most of the fractures occurred early on, but were still not uncommon as long as 5 years after the transplant operation, is consistent with findings relating to bone mineral content. Aird & Pierides found reduced values in 57 per cent of their patients 6 months after the transplantation, but in only 17 per cent at 30 months,[2] while Madsen and associates were still recording low levels after 6 years.[70] The absence of any correlation between the occurrence of fracture in the present series and sex, age, renal disease, duration of dialysis or postoperative care extends to BMC loss in the study by Aird & Pierides.[2]

The sites of fracture in the present study are also in agreement with those reported for other series.[43,65]

AETIOLOGY OF AVASCULAR NECROSIS

The results of earlier studies in which attempts have been made to identify factors responsible for avascular necrosis have been contradictory. In some cases the reason for this might well be that the short follow-up times did not permit of a reliable comparison; the median time for the development of avascular necrosis was 12 months (Study II), and in all but 4 of the earlier studies[5,20,86,91] the follow-up time did not exceed 6 months. Another source of unreliability is the small size of the series and, moreover, the fact that the multiple *t* test has been the only statistical method used. In the present large series of recipients whose grafts had functioned for more than 12 months the statistical analysis was performed by a multivariate test method, namely, discriminant analysis (Study III).

Clinical factors: Since avascular bone necrosis has been reported to occur during dialysis, the importance of renal osteopathy *per se* has been discussed.[7] However, there is no histological evidence that renal osteodystrophy is more severe or persistent in patients with avascular necrosis,[79] and no association has been found between the duration of uraemia and the occurrence of avascular necrosis.[5,30,86] In common with other workers[14,52,65] we have been unable to confirm the observation of Arfi[5] and Nielsen[79] that the dialysis time was longer for the patients with avascular necrosis (Study III); none of our patients developed this complication during dia-

lysis (Study II).

In two series unilateral avascular necrosis of the femoral head usually occurred on the side of the graft.[46,83] By way of explanation it was suggested that ligation of the hypogastric artery could compromise the blood supply to the femoral head. However, no support for this view is furnished by the present series, where unilateral necrosis occurred just as often on the contralateral side (Study II).

Antacid agents: The analysis of serum phosphorus in the groups treated with phosphate-binding and non-phosphate-binding antacid agents indicates that the former can have a bearing on the development of hypophosphataemia after transplantation (Study V). This is consistent with the results of earlier studies of renal graft patients.[4,93] In one study, however, it was doubted whether hypophosphataemia had a dietary causation, since the recipients were normocalcaemic.[62] Hypophosphataemia of dietary origin has, however, been reported in association with normocalcaemia,[68] and coexisting normocalcaemia may also be ascribed to the steroid treatment.[57] The low serum phosphorus level that we found in the renal graft recipients developing avascular necrosis (Study III) is consistent with the results reported by Briggs and by Potter.[14,87] It has been demonstrated that renal graft recipients with hypophosphataemia after renal transplantation tend to develop osteomalacia.[62,74] A lower bone density has also been found in recipients that later developed avascular necrosis.[66,73] The view that hypophosphataemia has a bearing on the occurrence of avascular necrosis therefore finds support in the correlation between the presence of hypophosphataemia and the presence of unmineralized bone tissue observed in biopsy studies,[81] and in the association between phosphaturia and bone loss after transplantation found in densitometric studies.[66]

Our results thus suggest that the use of phosphate-binding antacids increases the risk of avascular necrosis by creating hypophosphataemia. Support for this view is found in the observation that avascular necrosis was eliminated when the steroid doses were reduced and phosphate-binding antacids were replaced by non-phosphate-binding agents in most of the patients with hypophataemia (Study V).

Hyperparathyroidism: The phosphorus depletion observed after transplantation might conceivably be due to an increased renal clearance of phosphate due to either hyperparathyroidism or steroids, or both.[54] We found no correlation between the steroid dose and the presence of hypophosphataemia (Study III), and this condition was unaffected by lowering the steroid dose without simultaneous changeover to non-phosphate-binding antacids (Study V).

The results of PTH determinations in renal graft recipients have not disclosed any relationship between the serum concentration of PTH and phosphorus.[62,81] This together with the results of serum calcium determinations (Study III) suggests that the hypophosphataemia was not due to hyperparathyroidism. On the other hand, there is evidence from other sources that this disease can be responsible in some degree for the phosphorus depletion observed after transplantation even in the presence of normocalcaemia; for the slow establishment of normal renal function, which we found to be associated with an elevated incidence of avascular necrosis (Study III), may delay the development of hypercalcaemia.[97] In addition, glucocorticoid treatment, which will often correct hypercalcaemia in association with normal or low PTH levels, has also been reported to exert this effect in patients with hyperparathyroidism;[27] and according to Alfrey and collaborators the development of hypercalcaemia in hyperparathyroidism will probably be delayed until a critical level of phosphorus depletion has been reached.[4] The occurrence of such a normocalcaemic form of hyperparathyroidism might account for the observed high incidence of osteitis fibrosa lesions in patients with avascular necrosis.[7,14] The absence of avascular necrosis in those patients of a series that had required parathyroid surgery prior to transplantation also supports the view that hyperparathyroidism is a factor in the development of avascular necrosis.[105]

Steroids: Steroid therapy has been a central theme of discussions on the aetiology of transplantation osteonecrosis, for one reason because this condition has been observed in patients taking steroids for diseases that are not themselves considered to give rise to avascular necrosis.[35] In our study no correlation was found between the patients' individual steroid dose and the occurrence of avascular bone necrosis during the first year after the operation (Study III). This observation, which has been reported by a number of other workers,[5,11,21,53,87,91,103,104] might be interpreted as evidence that the development of osteonecrosis is unrelated to the steroid dose. Against this, however, is the association between the individual steroid dose and the development of avascular bone necrosis observed in some studies.[14,50,86] Since rejections and repeated transplantations necessitate periods of intensified steroid therapy, the association between these events and avascular necrosis observed in some series provides indirect support for the aetiological significance of steroid therapy.[49,99] Further evidence of such a relationship may be found in the observed reduction in the incidence of osteonecrosis following a decrease in the steroid dose.[49,77,87,106] It is of interest that in one of these studies,

too, there was no correlation between the individual steroid dose and the occurrence of avascular bone necrosis.[87] The findings of the present investigation (Study V) are consistent with those of the 4 previous studies; in these, however, the follow-up times for the groups are not matched, and in one of them[49] the incidence of avascular necrosis among the patients receiving the lower dose reached 10 per cent at a follow-up 2 years later.[7]

In a compilation of several renal transplant series where adequate information on dose could be obtained the critical dose of prednisone that differentiated the treatment groups with a high and a low incidence of avascular osteonecrosis was found to be about 100 mg/d during the first month after the operation.[53] This finds support in the results of the present study, where the complication was avoided when the dose was reduced from about 100 to about 60 mg/d (Study V).

It is, however, evident from this and other studies[86,87,91,103] that avascular bone necrosis can develop in patients who experience no rejection episodes and who receive a relatively small dose of prednisone, but that on the other hand, the complication need not develop in patients who experience rejection episodes and who take massive doses of prednisone. This considerable variability in the susceptibility of renal transplant patients to avascular necrosis may explain why, despite a decrease in the incidence of avascular necrosis following the reduction in the steroid dose (Study V), we found no correlation with the individual dose (Study III); this suggests that the developinent of avascular bone necrosis is dependent on other factors besides the intake of steroids.[42]

From the results of the present investigation it would appear that one such factor is phosphorus depletion, arising from the use of phosphate--binding antaçids or from secondary hyperparathyroidism, or both; this can affect the skeleton directly[88] or via synthesis of 1,25-dihydroxycholecalciferol.[51,93] As regards the mechanism for the action of the steroids the most widely held view is that the use of this agent leads to ischaemia and bone necrosis either by producing hyperlipidaemia, fatty liver and fat embolism[22,36,56] or by inducing osteopenia and microfractures.[95] There is no convincing proof for the correctness of either of these views,[42] nor does the present study furnish any support for them. Fatty liver was rare in the series; morover, that steroid osteopenia and and microfracturing are causes of avascular necrosis would appear unlikely in view of the fact that lowering of the steroid dose led to a decrease in the incidence of avascular necrosis but not of fracture (Study V) while an increase in the steroid dose after transplantation reduces the risk of fractures (Study IV).

PATHOGENESIS OF SPONTANEOUS FRACTURE

A continuous reduction in bone mass after renal transplantation has been demonstrated by histomorphometric methods,[16] radiographic spectrophotometry [26] and photon absorptiometry.[66] This is consistent with the increase in the incidence of spontaneous fracture after transplantation observed in this investigation (Study II): a correlation between the occurrence of fractures and the bone loss after transplantation has been demonstrated earlier.[2,80]

Osteomalacia: Osteomalacia fractures are rare,[43] and in Aird's biopsy study of 19 recipients sustaining spontaneous fractures there was no evidence of this complication.[2] Since there is histological evidence of early regression of osteomalacia after transplantation[19,33] it is improbable that this condition can account for the elevated incidence of spontaneous fracture in graft recipients.

Steroid-induced osteopenia: Since biopsy studies have also shown regression of osteitis fibrosa after transplantation[16,107] the continued loss of bone mineral has been generally considered to be steroid induced.[16,19,61,75] This interpretation, however, finds no support in the studies of bone mineral content and steroid consumption after transplantation, for these have not demonstrated any relationship.[2,26,66,75,82] The results of the present investigation, which indicate a significantly lower steroid intake during the first 3 months after the transplantation by patients sustaining fractures, are inconsistent with the view that the presence of steroid-induced osteopenia at this time is the reason for the high incidence of spontaneous fracture (Study IV). Further evidence against this prevailing view is the fact that the lowering of the steroid dose was not followed by a reduction in the incidence of spontaneous fracture (Study V). On the other hand, it is not improbable that maintenance doses of steroids are of importance for the low bone mineral content recorded some time after the transplantation.[55]

Osteitis fibrosa: Taken together, the examination by osteodensitometry and the observations of bone morphology and bone metabolism demonstrate that the decrease in the bone mineral content is greatest during the first few months after the transplantation,[2,26] and that the bone resorption is then more severe than prior to the operation.[48,78] The morphological studies, which were performed a longer time after the transplantation and which show regression of osteitis fibrosa alterations,[16,107] coincided in time with the reduction in, if not the arrest of, the loss of bone mineral.[2] These conditions may well be ascribed to the fact that the secondary hyperparathyroidism – which has still not regressed a few months after the transplantation

[38] – may then exert a stronger effect on the bone as a result of an increase in the sensitivity to parathyroid hormone,[60,88,97] following the onset of mineralization of osteoid tissue[19,33] and synthesis of 1,25-dihydroxycholecalciferol[51] after the transplantation. The view that the postoperative loss of bone is due to reinforcement of the secondary hyperparathyroidism by the effect of the transplantation on vitamin D metabolism, is not inconsistent with the observed regression of osteitis fibrosa after supply of the graft,[16,107] since these studies were carried out at times when the secondary hyperparathyroidism is considered to have regressed.[38]

It may seem paradoxical that the patients receiving the largest amounts of steroids over the first 3 months after the transplantation were less prone to sustain fracture (Study IV). Yet it supports the hypothesis advanced here concerning the pathogenesis of bone loss after the transplantation, since cortisone in high doses is known to inhibit bone resorption.[55,89,90,92,102] That prednisone can exert an effect antagonistic to PTH was reported by Eliel in 1965 in respect of hypoparathyroid patients treated with parathyroid extract and prednisone.[29] In later *in vitro* experiments with ^{45}Ca-labelled embryonal bone it was found that high doses of glucocorticoids inhibit PTH stimulated release of the isotope.[88,89,90,99] This has been confirmed in bone resorption studies *in vivo*.[63,88,102] In studies of the effect of various doses of cortisone on the metabolism of ^{85}Sr in the rat Jee and associates found a dose-dependence, the resorption of tibial metaphyseal bone being increased at low doses and decreased at high doses.[88] Furthermore, in studies of the effect of cortisone on periodontal ligament fibroblasts (precursor cells of bone) low doses were found to increase progenitor cell proliferation, the number of osteoclasts and resorption of alveolar bone, while high doses reduced progenitor cell proliferation and bone formation with no evidence of an increase in alveolar bone resorption. Eliel's view that prednisone affects PTH at the biochemical sites of action is borne out by these results and by the observation that high doses of cortisone depress the mobilization of ^{85}Sr from bone without there being any effect on the physiological functions by PTH and thyrocalcitonin.[102] The fact that the difference in the cortisone doses applies only to the first 3 months (Study IV) may be ascribed to the time dependence of this inhibitory effect of high doses of cortisone on bone resorption demonstrated by Kukreja and associates.[63] In their study of intact and parathyroidectomized rats they found that the effect of cortisone in reducing bone resorption was overtaken after 12 - 17 weeks by a compensatory rise in PTH secretion in the intact animals.

TREATMENT OF AVASCULAR NECROSIS

Surgical treatment was required only in cases where the femoral head was involved (Study II). This is consistent with the experience of other transplantation units where surgery for osteonecrosis of the knee[1,47,49,64] and the humeral head[23,104] was resorted to only in exceptional cases.

Our results in patients with total hip replacement, in common with those obtained in other series,[24,76] indicate that the risk associated with major hip surgery in the renal graft recipient is an acceptable one. Since the results obtained with this surgical method have been excellent[30,45,64,87,92,99,104] we are inclined to agree with Gustafsson and associates that total hip replacement should be recommended to the post-transplant patient who is much troubled by pain and where there is radiographic evidence of avascular necrosis of the femoral head.[45] With the low-friction arthroplasty techniques available today the risk that the prosthesis will loosen is probably not greater for these patients than it is for others.[18] Moreover, the risk of infection can be minimized by administering prophylactic antibiotics[45] and by using special ventilation systems in the operating theatre.[92]

For series where the follow-up time has been reported the results obtained with femoral head prostheses have been poor owing to migration of the prostheses in the osteopenic bone.[24,30,76] Troch and collaborators[103] report satisfactory results obtained with cup arthroplasty at very early stages of avascular necrosis; otherwise they had no success with the method, and Cruess likewise.[24] The early and aggressive treatment often advocated for traumatic avascular bone necrosis[34,96] would seem to be inappropriate for osteonecrosis following transplantation, since less than one half of the patients later developing subchondral collapse required surgery.[24] Moreover, in only a few series have early stages of avascular necrosis been treated with less radical measures such as drilling, cortical bone graft and osteotomy.[24,64,72,76] The osteotomy material is too small to permit of any meaningful evaluation.[24] The results obtained with cortical bone graft are by no means consistent, besides which the method is probably unsuitable owing to the severe osteopenia affecting the viable bone of the femoral head in these patients.[96]

TREATMENT OF SPONTANEOUS FRACTURE

As union occurred within the normal time in all our patients and no complications were encountered during the period covered by the treatment, we see no reason to recommend for this type of patient any departure from the comventional management of fractures (Study II).

GENERAL SUMMARY AND CONCLUSIONS

In a large series of renal graft recipients with a long graft survival the occurrence of skeletal complications was examined with special reference to their incidence, clinical features and treatment. To examine whether there are factors that induce susceptibility to these complications patient groups with and without them were compared with respect to various clinical factors, immunosuppressive therapy and the results of biochemical analyses during the first year after the transplantation. In the statistical treatment of the findings discriminant analysis was used. The effect of attempts to avoid factors found to increase the risk of skeletal complications was also examined.

Spontaneous fractures were sustained by 26 per cent of the patients, and osteonecrosis was detected in 11 per cent. These presented major clinical problems, and were sometimes the only obstruction to complete rehabilitation of the graft recipients. The skeletal complications were equally common among the male and female patients; they were more common at higher ages. They occurred to the same extent whether the donor of the graft kidney was a living relative or a deceased person. They were not more common among patients receiving their second or third graft kidney. The first spontaneous fracture occurred between 1 and 58 months after the transplantation and was usually located in the pelvis. The treatment followed standard principles and union was obtained with no complications. Osteonecrosis appeared between 5 and 46 months after the transplant operation and was often multifocal, with the femoral head as the commonest site. Surgical intervention was required only when the femoral head was involved; in the cases where total hip replacement was performed the results were excellent.

The steroid doses were lower for the fracture patients during the first 3 months after the transplantation ($P < 0.01$). This applied to the oral prednisone intake, the total intake of steroids (oral prednisone and intravenous methyl prednisolone) and the mean daily intake of these drugs in relation to weight and body surface area.

The serum phosphorus concentration 2 months after the transplant operation was lower in the group with osteonecrosis ($P < 0.01$); stepwise discriminant analysis disclosed that the incidence of osteonecrosis increased with age and inversely as the rate of normalization of renal function. After the prednisone dose had been lowered ($P < 0.00001$) and phosphate-binding

antacids had been replaced by non-phosphate-binding agents in most of the recipients with hypophosphataemia, none of the recipients developed osteonecrosis ($P < 0.1$), but there was no decrease in the incidence of spontaneous fracture.

The recipients given non-phosphate-binding antacids showed a higher serum phosphorus concentration than those given phosphate-binding agents ($P < 0.005$).

On the basis of the above results the following conclusions have been drawn.

Spontaneous fracture is more likely to occur after than before transplantation, and the risk is considerably greater than has been inferred from the earlier studies with a shorter follow-up period.

This greater proneness to spontaneous fracture is probably due to an increase in bone resorption arising from enhanced sensitivity of the bone to the effects of secondary hyperparathyroidism. This greater sensitivity is due to the mineralization of osteoid tissue and the production of 1,25 dihydroxycholecalciferol, which starts after transplantation.

A high dose of steroids furnishes temporary protection against this bone resorption.

Osteonecrosis is a fairly common complication of renal transplantation, and it can prejudice the patient's rehabilitation.

Older recipients with slower normalization of renal function and severe hypophosphataemia in the early posttransplant period run a greater risk of developing osteonecrosis.

Phosphate depletion after renal transplantation, whether dietary or due to secondary hyperparathyroidism, or both, together with untoward effects of steroids tend to promote the development of osteonecrosis.

The tendency for steroids to induce osteopenia has no significant bearing on the occurrence of osteonecrosis.

For renal graft recipients with severe symptoms from osteonecrosis of the femoral head total hip replacement may be recommended. The associated surgical risk is acceptable.

Osteonecrosis in the renal graft patient may be avoided by reducing the dose of steroids and by administering non-phosphate-binding antacids.

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