typers, and others who contributed to this programme of transplantation between 1965 and 1972.

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# Effects of Age, Sex, and Polycystic Disease on Progressive Bone Disease of Renal Failure

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*British Medical Journal*, 1974, **4**, 557-560

## Summary

**A study of 150 patients undergoing haemodialysis has shown that age had a striking effect on the radiological presentation of renal bone disease, erosions being common in the young and uncommon in older patients and vascular calcification showing opposite trends to this. Men aged 20 to 59 years had a greater tendency to develop erosions than did women in this age range. Examination of a group of 53 patients over a period of five years showed that the half time for the development of vascular calcification was 4·6 years, erosions 26·7 years, and fractures 6·9 years. Nine out of 16 polycystic patients matched for age and sex with 50 controls did not develop erosions and had consistently less vascular calcification than the controls when examined over a six-year period.**

## Introduction

In a previous study (Tatler *et al.*, 1973) we described the rate of progress of renal bone disease in 135 haemodialysis patients over a period of 10 years. The results indicated that the disease was progressive, with half times ($t\frac{1}{2}$) for the development of vascular calcification, erosions, and fractures of 3·4, 22·9, and 9·1 years respectively. In the present study subgroup analysis was performed on 150 patients in order to determine the effects of age and sex on these lesions. A cohort of 53 patients was examined over a complete period of five years of treatment. An opportunity was also taken to examine the effect of polycystic disease on the progress of radiological lesions.

## Present Study

The 150 patients were all on the haemodialysis programme, and haemodialysis techniques, dietary management, and use of phosphate binders were as previously described (Moorhead *et al.*, 1969; Tatler *et al.*, 1973).

Cadaveric renal transplantation was performed in some of the patients, who were removed from the study when this was successful. Most patients in whom transplantation was unsuccessful were returned to the study and continued with dialysis. Bilateral nephrectomy was performed in only three patients and total or subtotal parathyroidectomy in four.

*Radiological investigations* were performed as previously described (Tatler *et al.*, 1973), and in the present study we were concerned principally with vascular calcification, erosions, and fractures. Radiographs were obtained at the start or within a few months of the start of haemodialysis.

*Cohort of 53 Patients.*—These patients had been on dialysis for five or more years. Their radiographs were examined at six-monthly intervals during the first five years for the presence of vascular calcification, erosions, and fractures.

*Age and Sex.*—Differences in the incidence of the three lesions in male and female patients were sought. The six age groups examined were 0-9, 10-19, 20-29, 30-39, 40-49, and 50-59 years.

*Patients with Polycystic Disease.*—As a result of the observation that certain radiological manifestations of renal bone disease seemed less frequent in this group nine of the 16 patients with polycystic disease were separately analysed. Six were excluded because of coexistent pyelonephritis, transplantation, or inadequate data. Of the remaining 10 patients, nine were men, and these were compared with 50 other men in the age group 30-59 years.

*Method of Analysis.*—The percentage of patients with each lesion at successive years of treatment up to 10 years was calculated. Subgroup analysis of the groups mentioned above inevitably reduced the number of patients, and tests for statistical validity were confined to the larger groups. The results of these analyses are given when they seem to be particularly relevant. Throughout, the analyses include all patients except when individual subgroups contained fewer than five.

## Cohort of 53 Patients

The mean age of these patients at the start of haemodialysis was 34·15 years. The proportions with fractures, vascular calcification, and erosions one, two, three, four, and five years later are shown in fig. 1, in which the mean starting age is used as the starting point for each curve. By extrapolating the curves to the point at which 50% of the patients would be expected to develop lesions the number of years for this development to take place can be estimated. The estimates for the development time of vascular calcification, fractures, and erosions were 4·6 years, 6·9 years, and 26·7 years respec-

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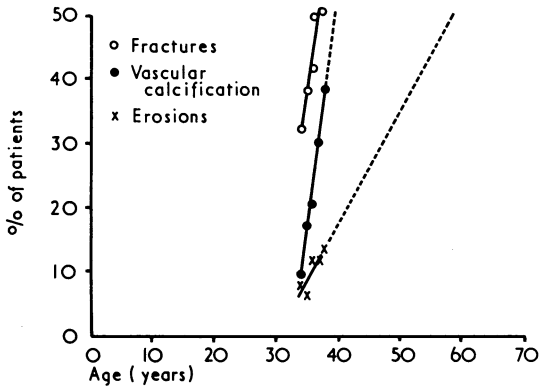


FIG. 1—Cohort of 53 patients. Percentage with vascular calcification, erosions, and fractures one, two, three, four, and five years after starting haemodialysis. Starting point is mean age (34·15 years) for group. Dashed lines indicate extrapolation to time at which 50% of patients would be affected.

TABLE I—*Mean Age at Start of Haemodialysis and Half Times ($t\frac{1}{2}$) for Development of Bone Lesions in Cohort of 53 Patients and in 135 Patients Studied Previously (Tatler et al., 1973). (Method of Analysis in Each Group was Different*

| No. of Patients | Mean Starting Age (Years) | $t\frac{1}{2}$ (Years) | | |
|---|---|---|---|---|
| | | Vascular Calcification | Erosions | Fractures |
| 53 | 34·15 | 4·6 | 26·7 | 6·9 |
| 135 | 34·7 | 3·4 | 22·9 | 9·1 |

tively. These findings are compared with estimates in our previous series of 135 patients (Tatler *et al.*, 1973) in table I.

## Whole Group of 150 Patients

### AGE

*Vascular calcification* (fig. 2) showed a striking age relationship at the start of dialysis, with a rapid subsequent increase in the proportion of patients in each group. The curve for patients aged 20 to 29 years did not appear to fit well with the others.

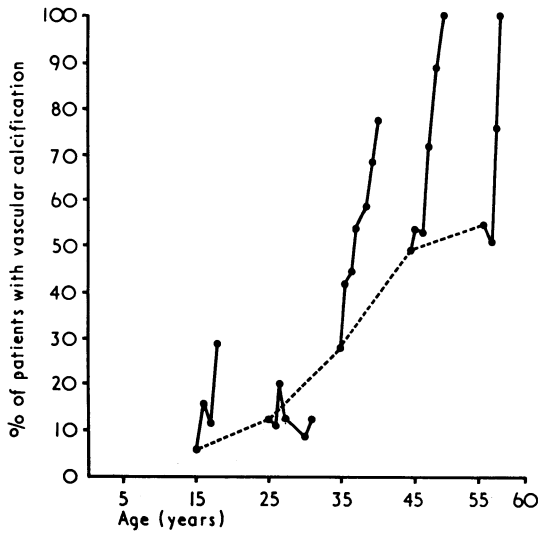


FIG. 2—Whole group of 150 patients. Percentage with vascular calcification at start of dialysis and yearly thereafter in five age groups. Dashed line connects percentages for each group at point at which dialysis began, indicating effect of age on lesion.

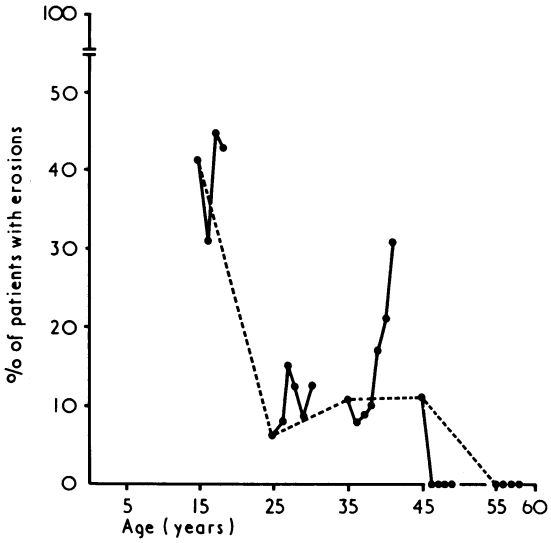


FIG. 3—Whole group of 150 patients. Percentage with erosions at start of dialysis and yearly thereafter in five age groups. Dashed line connects percentages for each group at point at which dialysis began, showing effect of age on lesion.

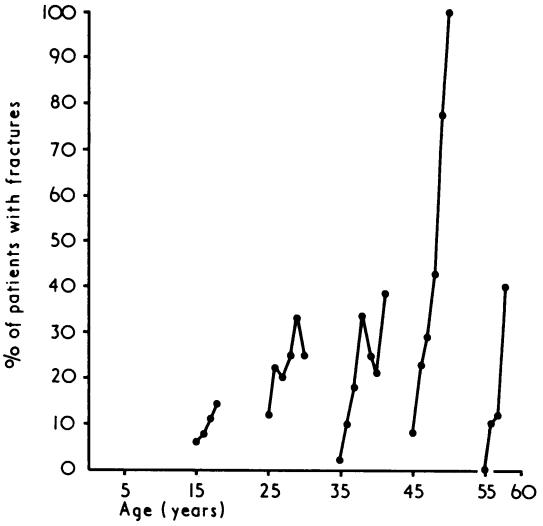


FIG. 4—Whole group of 150 patients. Percentage with fractures at start of dialysis and yearly thereafter in five age groups.

*Erosions* (fig. 3) showed an equally striking age relationship at the start of dialysis, with the highest percentage occurring in the young. No erosive changes were seen in patients over 50.

*Fractures.*—The proportion of patients with fractures at the start of dialysis and the increase with time on dialysis appeared to be similar in all age groups (fig. 4).

### SEX

*Vascular Calcification.*—The overall picture for vascular calcification was similar in both men and women with no significant differences emerging with age.

*Erosions.*—In the 0-19-year age group there were equal numbers of male and female patients with erosions. Subsequently these occurred more often in men. In patients aged 20 to 59 years the proportion of women with erosions was 2·2% (1/46) and the proportion of men 12·2% (10/82) ($P < 0·04$).

*Fractures.*—In patients aged 30 to 59 years fractures occurred consistently more often in men than in women in

each year of study. These differences were not apparent in the younger groups.

COINCIDENCE OF RADIOLOGICAL FACTORS

An analysis of the 150 patients was performed for vascular calcification, erosions, fractures, Looser's zones, vertebral osteosclerosis, and periarticular calcification for one to 10 years. No two lesions occurred together more often than would be expected by chance with the exception of erosions and vertebral osteosclerosis, which were highly correlated ($P < 0.00001$).

## Patients with Polycystic Disease

Nine men with polycystic disease were compared with a group of 50 dialysis patients without polycystic disease matched for age and sex. Differences emerged in the proportion of patients with vascular calcification (fig. 5) and erosions (fig. 6). Consistently fewer polycystic patients than controls developed vascular calcification in each year of study and none developed erosions.

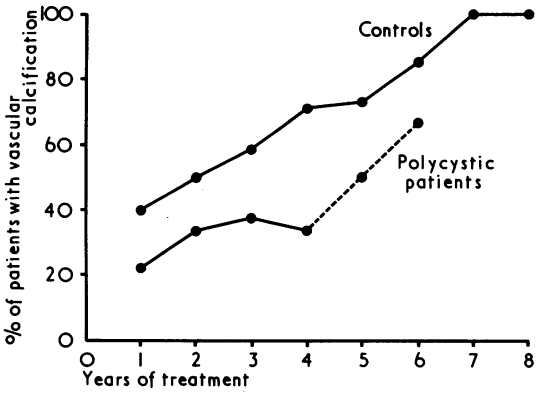


FIG. 5—Increase of vascular calcification in nine male polycystic haemodialysis patients and 50 controls matched for age and sex. Five patients had up to four years of treatment, dashed line indicating fewer than five patients. Polycystic patients showed consistently less calcification.

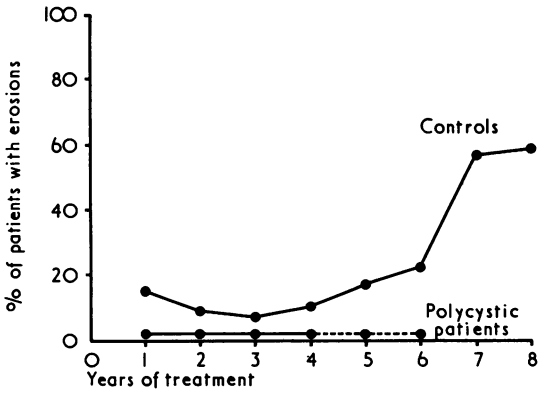


FIG. 6—Incidence of erosions in 50 controls matched for age and sex with nine male polycystic haemodialysis patients, none of whom had erosions. Five polycystic patients had up to four years of dialysis, dashed line indicating fewer than five patients.

## Discussion

These observations confirm our previous report (Tatler *et al.*, 1973) that bone disease is progressive in patients on the dialysis programme. The cohort of 53 patients was examined separately to demonstrate this point and to show that the increasing proportion of patients with lesions was not due to a diminishing number of patients in each year of study. The cohort remained constant in size and the proportion of patients with each lesion increased with time (fig. 1). Interestingly the $t_{\frac{1}{2}}$ for the development of each lesion in this subgroup was close to the previous estimate (Tatler *et al.*, 1973) though the two results were obtained by different methods. The reasons for the differences (table I) may lie in the disparity between the sample sizes (53 *v.* 135), the slightly different mean starting ages (34·15 *v.* 34·7), and the different age distributions. The estimates of $t_{\frac{1}{2}}$ were obtained by extrapolation (fig. 1). and are therefore approximate but the results of the analysis give confidence in the analytical method previously used.

There appeared to be a number of important age-related and sex-related characteristics of renal bone disease in the whole group of 150 patients. Five curves for vascular calcification, each relating to succeeding age groups, are shown in fig. 2. The first point on each curve indicates the percentage of patients with vascular calcification at the start of dialysis for each particular age group. This suggests that calcification of vessels occurs commonly in patients before dialysis starts and cannot be attributed to dialysis alone; furthermore, vascular calcification at the start of dialysis increases rapidly with age. The rate of increase of vascular calcification in patients with declining renal function before haemodialysis starts is unknown at present and is the subject of a separate study. Vascular calcification is often seen in certain major blood vessels in a hospital population of older patients. It seems likely, however, that the vascular calcification reported here was more than a 20-30-year shift to the left of the curve for the normal population. After dialysis began, the increase in patients with calcification was rapid in all age groups except 20 to 29 years. The explanation for this is not clear.

Marked age-related characteristics were also shown at the start of dialysis with erosions, the trend being opposite to that found for vascular calcification. The tendency to develop erosions fell rapidly with increasing age (fig. 3). Erosions were uncommon in women aged 20 to 59 years (2·2%; 1/46) compared with men (12·2%; 10/82) though none occurred in the nine men with polycystic disease. When these polycystic patients are excluded from analysis the proportion of men aged 30 to 59 years with erosions is 16% (8/50), which is significantly greater than the 2·8% (1/36) for women in this age group ($P < 0.047$). There is no immediate explanation for these differences since treatment was similar for all patients. Interestingly fractures appeared to be unrelated to age at the onset of treatment (fig. 4), only a small proportion of patients in each group having lesions at that time. Fractures developed at a similar rate in all patients after dialysis began.

Female sex may possibly confer some advantage with respect to erosions in the age range 20-59 years (women *v.* men: 2·2% *v.* 12·2%; $P < 0.04$). The role of polycystic disease in possibly protecting against erosions and vascular calcification is obscure. Though only nine male patients could be matched for age and sex with controls the fact that no erosions developed in polycystic patients and vascular calcification was consistently less in this group is of interest. There was a dip in the curve for erosions in the controls, which is explained by the fact that healing of erosions took place in some patients after dialysis, this effect being later obscured by an increase in the proportion of patients who developed this lesion. Mawer *et al.* (1973) showed that "negligible" amounts of 1, 25-dihydroxycholecalciferol were present in a polycystic patient's serum. This was not measured in our patients. A possibility is that the large polycystic kidney may be capable of binding or in some way modifying parathyroid hormone, thus preventing erosions.

Unfortunately there are still no other published data with which to compare all our findings. The results of five surveys

TABLE II—*Proportions of Patients Presenting with Erosions in First Year of Dialysis in Five Series*

| | No. of Patients | Proportion who Presented with Erosions | |
|---|---|---|---|
| | | No. | % |
| Tatler *et al.* (1973) | 135 | 16 | 11·9 |
| Johnson *et al.* (1967) | 33 | 8 | 24·2 |
| Cohen *et al.* (1970) | 29 | 6 | 20·7 |
| Simpson *et al.* (1973) | 11 | 1 | 9·1 |
| Platts *et al.* (1973) | 30 | 2 | 6·7 |
| Total | 238 | 33 | 13·9 |

TABLE III—*Data as in Table II but with Patients Under 20 Years of Age Excluded**

| | No. of Patients | Proportion who Presented with Erosions | |
|---|---|---|---|
| | | No. | % |
| Tatler *et al.* (1973) | 124 | 10 | 8·1 |
| Johnson *et al.* (1967) | 30 | 6 | 20·0 |
| Cohen *et al.* (1970) | 25 | 3 | 12·0 |
| Simpson *et al.* (1973) | 11 | 1 | 9·1 |
| Platts *et al.* (1973) | 28 | 2 | 7·1 |
| Total | 218 | 22 | 10·1 |

*Age under 20 years was associated with high incidence of erosions (see fig. 3).

giving information on erosions, however, have been assembled in table II, which shows the proportions of patients presenting with erosions in the first year of dialysis. When patients below 20 years of age are excluded (table III) the proportion presenting with erosions falls from 13·9% to 10·1%, which supports the observation that this lesion is commoner in young patients.

The results presented here call attention to the widely varying response of individual patients to renal failure and dialysis and emphasize that when comparing the results of radiological studies between different centres it will in future be essential to take into account the age and sex of the patients. Results of surveys within centres should also be evaluated with respect to the age at which dialysis was started and the average age of the group.

It now appears as a result of two different analyses that radiological bone disease in patients in this centre is indeed slowly progressive. We again emphasize, however, that bone disease is rarely symptomatic; even fractures would sometimes have been missed had regular skeletal surveys not been performed on all patients.

## Conclusions

Examination of the incidence of vascular calcification, fractures, and erosions in a cohort of patients after one and five years of dialysis has confirmed that these lesions are progressive in our patients, and this supports a concept of determining the relationship between rates of development of bone disease by comparison of the $t_{\frac{1}{2}}$ for each lesion.

The disturbing rate of increase in lesions in patients on dialysis previously reported cannot be held to be due to dialysis alone since we have now shown that age at the onset of dialysis and to some extent sex influence the frequency with which lesions are detected. The intrinsic renal disease may also play a part in the pathogenesis of renal bone disease, as suggested by the failure of the patients with polycystic disease to develop erosions.

It now appears that the role of dialysis itself in the pathogenesis of renal bone disease cannot be determined with precision since the proportion of pre-dialysis patients with lesions has not yet been studied in detail. Preliminary studies, however, suggest that radiological changes begin to appear with rapidity in the late stages of renal failure. Whatever the effects of dialysis itself and of the therapy to mitigate or prevent the lesions it is clear that the results of intervention of any kind must be interpreted with the factors described here in mind, since bias will result from ignoring them. For example, centres which offer dialysis to children and young people will experience a different pattern of bone disease from other centres. It also seems likely that the proportion of males to females will be of importance.

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# Combination Therapy for Myelomatosis

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*British Medical Journal*, 1974, 4, 560-564

## Summary

**Twenty-eight patients with multiple myeloma have been treated with a quadruple chemotherapeutic regimen consisting of 1, 3 bis (2-chloroethyl)-1-nitrosourea (BCNU), cyclophosphamide, melphalan, and prednisolone. Nineteen new patients and nine who had escaped from previous single-agent therapy were included in the study. The results to date, on eight criteria of response, seem to be superior to those obtained from previous chemotherapeutic regimens. The study has been in progress for 18 months and only three patients have died. Only one who had not received previous therapy died, and she had complicating hyperparathyroidism, which almost certainly contributed to her death.**

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## Introduction

Over the past 10-15 years various workers have shown the ability of several alkylating agents to improve the clinical state of patients with myelomatosis, with a resultant increase