PAPERS AND ORIGINALS

Evolution of Bone Disease over 10 Years in 135 Patients with Terminal Renal Failure

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Summary

An objective radiographic study of erosions, fractures, and periarticular and vascular calcification was made in a series of 135 patients over 10 years of maintenance haemodialysis therapy. The four lesions progressed at different rates, consistent with variation in the response of tissues to a changing biochemical milieu and deficiency in vitamin D metabolites. The half time for development of individual radiographic signs was 3·4 years for vascular calcification, 9 years for fractures, 16 years for periarticular calcification, and 22·9 years for erosions. Calcification of the dorsalis pedis artery seen as a developing ring or tube was an early and valuable sign of disturbed calcium metabolism. In these patients renal osteodystrophy is a chronic condition with a prolonged time course.

Introduction

The first recorded association between chronic renal failure and bone disease has often been ascribed to Lucas (1883). Virchow in 1855, however, described five cases of destructive disease of the skeleton associated with nephritis and also noted the occurrence of ectopic calcification.

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MacCallum (1905) described the first case of a parathyroid tumour in association with chronic nephritis, and Parsons (1927) observed the radiographical changes of osteomalacia and osteitis fibrosa. In the 1940s Ginzler and Jaffe (1941) noted osteosclerosis and Liu and Chu (1943) introduced the term renal osteodystrophy to cover all aspects of the bone disease associated with renal failure. More recently Pendras and Erickson (1966) drew attention to the florid form of renal osteodystrophy associated with long-term haemodialysis, and Doyle (1972) described the radiographic changes seen in chronic renal failure before and after the start of maintenance haemodialysis therapy.

Though it is clear that osteodystrophy is often well established when maintenance haemodialysis therapy is started many workers have emphasized that bone disease may progress with startling rapidity during treatment. Moreover, the wide variation in the radiographic and symptomatic presentations between different centres (O'Riordan *et al.*, 1970) has not been explained by careful study of factors such as local water supply, nutrition, and dialysis fluid composition (Siddiqui and Kerr, 1971).

In the present study a review of the radiographic features of renal osteodystrophy was undertaken to determine the time course of the syndrome in 135 patients treated in a single centre over a period of 10 years.

Patients and Methods

All 135 patients began haemodialysis between March 1963 and March 1973; 115 were alive at the completion of the study. Of the 20 deaths none, with the possible exception of one in a patient who developed pneumonia in the presence of recent rib fractures, were directly attributable to bone disease. Moreover, there was no indication that the patients who died represented a special group (Moorhead *et al.*, 1970). Altogether 80 of the patients were male and 55 were female (table I). Radiographical surveys were brought up to date at the close of the period of analysis.

Cadaveric renal transplantation was performed in 47 patients using 51 kidneys; at the end of the study 27 patients had a functioning transplant. The time during which the patient had a functioning transplant was not included when calculating the results. In the 20 patients who returned to dialysis after trans-

plant failure dialysis time was assumed for the purpose of analysis to be continuous.

One patient had a total parathyroidectomy three years before starting maintenance haemodialysis therapy; one total and two subtotal parathyroidectomies were performed after haemodialysis was started. These patients were not excluded from the analysis.

TABLE I—*Age and Sex Distribution of Patients*

Age (years)	Males	Females	Total
0- 9	2	2	4
10-19	2	5	7
20-29	13	11	24
30-39	29	13	42
40-49	17	19	36
50-59	16	4	20
60 and over	1	1	2
Total	80	55	135

HAEMODIALYSIS

The methods of maintenance haemodialysis therapy have been described previously (Moorhead *et al.*, 1970). The renal failure programme is based on home dialysis though some patients were dialysed in hospital throughout the study period. Access to the blood stream was by internal arteriovenous fistulae or external Teflon-Silastic shunts. Patients were dialysed for 30 hours each week in three 10-hour overnight sessions using a standard 0·9-m² Kiil dialyser and individual automatic monitors. Hypertension was treated by gradual ultrafiltration and sodium restriction together with much-improved nutrition (Craswell *et al.*, 1972). Bilateral nephrectomy was not resorted to except in unusual circumstances, being performed in only two of the patients in this series. A high degree of social, occupational, and educational rehabilitation was encouraged and was attained by most patients (Baillod *et al.*, 1969).

DIALYSIS FLUID COMPOSITION

Apart from the calcium content variations in dialysis fluid composition were small during the period of study. Calcium concentration was gradually increased from 2·5 to 3·75 mmol/l. between 1963 and 1972 (table II). The dialysis fluid concentrate was diluted 40/1 with softened water by the metering pump of the individual monitors to final electrolyte concentrations of: sodium 130-137 mEq/l., calcium 3·75 mEq/l., potassium 1·34 mEq/l., magnesium 2·00 mEq/l., chloride 102 mEq/l.

TABLE II—*Dialysis Calcium Concentrations in mmol/l. at Successive Periods during* 1963-72

Dialysis Calcium Concentration mmol/l.	Period of Use	Treatment Years
2·5-3·2	1963-6	1-3
3·2-3·3	1967-9	4-6
3·75	1970-2	7-9

DIET

Estimates of the constituents of diet are invariably subject to considerable error; however, analysis of prescribed diets gave an approximation to dietary calcium intake. No evidence was found that bone disease occurred more often in patients with a calcium intake of less than 500 mg/day. Aluminium hydroxide was prescribed to all patients in doses of 4-6 g/24 hours. In the case of children the dietary calcium was increased by the addition of calcium supplements (Baillod *et al.*, 1972). The diet was supplemented by intravenous iron and vitamins.

RADIOGRAPHICAL PROCEDURES

Assessment

At the start it was evident that evaluation of many of the radiographical features of renal osteodystrophy was subjective. Also useful comparison of radiographs in the same patient over a number of years and between patients with the same radiographic signs was made impossible by changes in the type of equipment, *x*-ray film, and exposure factors. It was therefore decided to consider a limited range of abnormalities and to record only whether they were present. The degree of severity of a lesion was noted for clinical purposes but no analysis of severity was made. The lesions assessed were erosions, fractures, vascular calcification, and periarticular calcification. Other changes such as loss of bone density, cystic lesions, and sclerosis were noted but were not analysed for this survey.

Serial radiography of patients over a period of years made it possible to determine the time after dialysis started at which each sign appeared. It was of particular interest that in a proportion of patients some lesions were already present radiographically at the start of dialysis.

Method

Patients had a routine six-monthly radiographic survey of the chest, lumbar spine, pelvis, hands, feet, and mandible. The details of the survey varied slightly over the years. For example, earlier studies often omitted the feet. Later the temporomandibular joints and intraoral views of the teeth were included, while the skull and mandibular views were omitted. In each patient clinical circumstances required radiographs of other areas supplementary to the six-monthly survey in this study. Comparatively few radiographs were lost to follow-up.

All films were seen and assessed by G.L.V.T. and by at least one other person.

Unfortunately few radiographs were available for the predialysis renal failure period, so that no predialysis assessment could be made either individually or for the group as a whole. The radiographs taken in the first year of haemodialysis, however, did allow an estimate of predialysis osteodystrophy. Thus the rate of increase of each lesion could be measured (figs. 1-4, table III).

TABLE III—*Years on Dialysis and Percentage of Patients with Each Lesion*

No. of Years on Dialysis	No. of Patients	Erosions	Periarticular Calcification	Vascular Calcification	Fractures
<1	135	12%	9%	27%	7%
-2	112	10%	14%	37%	12%
-3	91	14%	14%	46%	19%
-4	74	15%	20%	53%	28%
-5	55	18%	22%	58%	33%
-6	37	16%	19%	62%	38%
-7	25	36%	28%	80%	40%
-8	15	40%	47%	87%	47%
-9	12	50%	42%	83%	50%

ANALYSIS OF RESULTS

Patients were arranged in groups according to their years on maintenance haemodialysis therapy. None of the patients who presented with one of the four lesions under study at the start of dialysis were left out (table III). This inevitably resulted in the inclusion of predialysis lesions but there was no way of excluding such patients. Since only four patients had completed

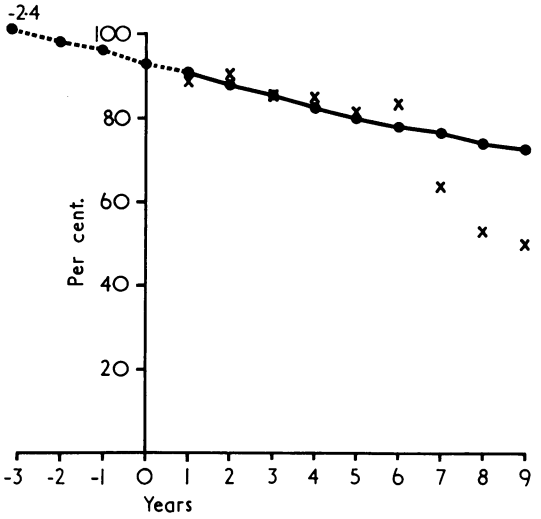

FIG. 1—Percentage of 135 patients without erosions *v.* years of treatment. ● = Computer-fitted. x = Observed data. -- = Extrapolated.

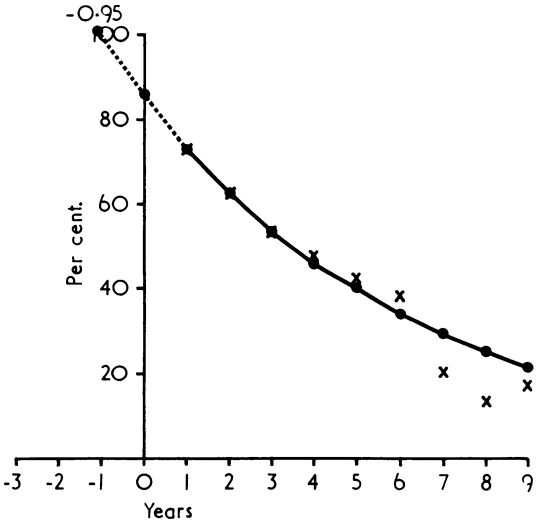

FIG. 2—Percentage of 135 patients without vascular calcification *v.* years of treatment. ● = Computer-fitted. × = Observed data. -- = Extrapolated.

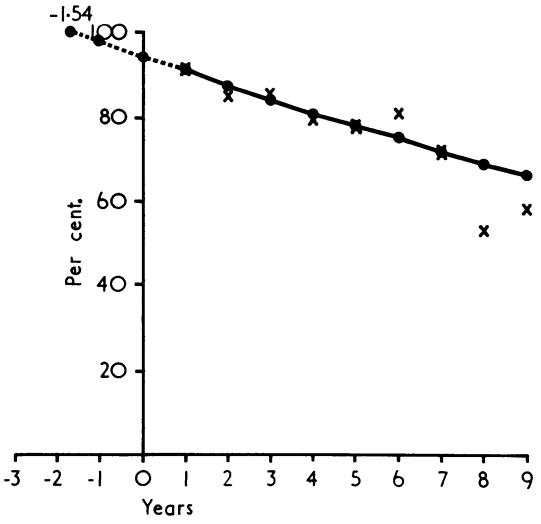

FIG. 3—Percentage of 135 patients without periarticular calcification *v.* years of treatment. ● = Computer-fitted. x = Observed data. -- = Extrapolated.

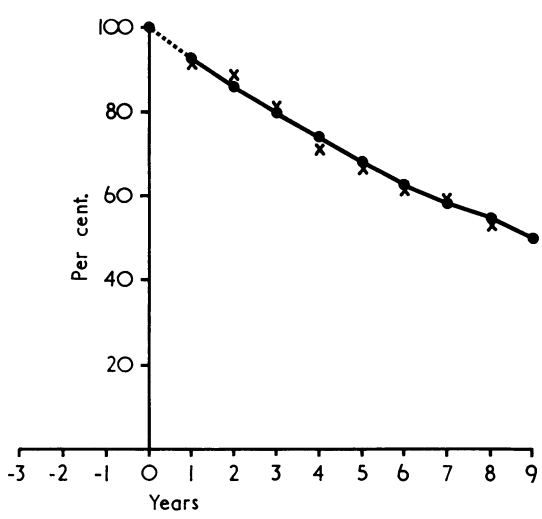

FIG. 4—Percentage of 135 patients without fractures *v.* years of treatment. ● = Computer-fitted. x = Observed data. -- = Extrapolated.

10 years of treatment the analysis of results was not continued beyond the ninth year.

The observed percentages of each lesion were plotted together with a computer-fitted curve obtained from the same data using the method of weighted least squares (figs. 1-4). By using these curves it was possible to read off the time when each lesion would be expected to develop in 50% of the patients ($t_{\frac{1}{2}}$) (table IV). The slow rate of development of periarticular calcification and erosions made it necessary to calculate the $t_{\frac{1}{2}}$ of these lesions by extrapolation of the computer-fitted curves. It was also found possible to extrapolate the curves to the predialysis period and to estimate the time at which each lesion appeared (table IV).

TABLE IV—*Half Time for Each Lesion and Estimated Time of First Appearance in 135 Patients*

	Erosions	Periarticular Calcification	Vascular Calcification	Fractures
$t_{\frac{1}{2}}$ in Years	22·9	16·7	3·4	9·1
Estimated first appearance in years	−2·40	−1·54	−0·95	+0·13

Results

EROSIVE CHANGES

Evidence of osteitis fibrosa was sought in subperiosteal and subchondral sites throughout the skeleton. Subperiosteal erosions were found most often along the radial borders of the phalanges of the hand, the phalanges of the feet, the metatarsals, the femora, and the pelvis. The acromioclavicular, sacroiliac, and temporomandibular joints and the pubic symphysis were also often involved. When erosions were present in a number of different sites they were always well marked in the phalanges of the hand. Bone rarefaction and cyst formation were often noted but no objective assessment was possible.

Subperiosteal erosions healed completely in two patients within two years of starting treatment. The increase in erosions was gradual, the $t_{\frac{1}{2}}$ for this lesion being 22·9 years (fig. 1, table IV). The computer-fitted curve closely approximated to the observed data except in the final years of treatment, probably because relatively few patients were considered for this time.

Though the $t_{\frac{1}{2}}$ for erosions was prolonged the lesions were severe in several of the affected patients.

The acromioclavicular joint was widened in four patients with erosion of the lateral ends of the clavicles. Five patients, including the four with clavicular disease, had marked widening of the pubic symphysis, and in six sacroiliac joints were also widened. The temporomandibular joint was found to have underlying varying degrees of erosion in six cases (Dick and Jones, 1973). Evaluation of loss of the lamina dura was not made since intraoral views had not been obtained in enough cases.

METASTATIC CALCIFICATION

This complication was seen in two main sites—in the blood vessels and in soft tissue around the joints.

Vascular calcification increased more rapidly than any other lesion, with 27% of the patients being affected in the first year of treatment (fig. 2). The $t_{\frac{1}{2}}$ for this lesion was 3·4 years (table IV). The earliest radiographical sign of disturbed calcium metabolism was calcification in the dorsalis pedis artery between the origins of the first dorsal metatarsal and the first plantar metatarsal arteries, where the dorsalis pedis artery descends to the sole of the foot between the first and second metatarsal bones. When calcified it was easily seen radiographically as a ring or a tube (fig. 5). In this series the ring or tube sign was positive in 46 out of 127 patients (36%). The first dorsal metatarsal artery was also frequently calcified. The sign occurred alone or with other signs as the first evidence of disease in 17 patients. Otherwise calcification was usually seen at the bifurcation of arteries. The division of the internal iliac artery into its anterior and posterior divisions was calcified in 43 (33%) of the 132 patients who had this area radiographed.

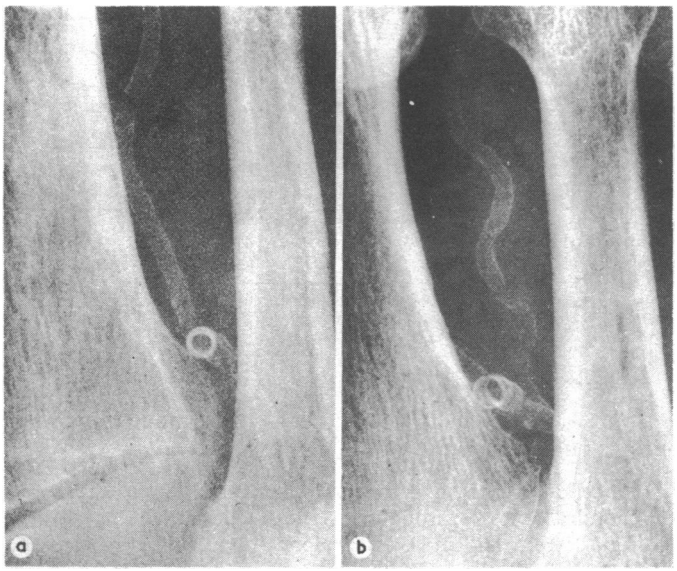

FIG. 5—Calcification in dorsalis pedis artery seen as ring (left) or tube (right).

Periarticular calcification increased slowly throughout the survey, with a $t_{\frac{1}{2}}$ of 16·7 years (fig. 3, table IV). It was often found in relation to small joints, especially in the hands, and when seen in relation to larger joints was occasionally massive (fig. 6). Calcification was sometimes seen in tendons, seminal vesicles, ovarian cysts, and kidneys, and the costal cartilages were often unusually heavily calcified.

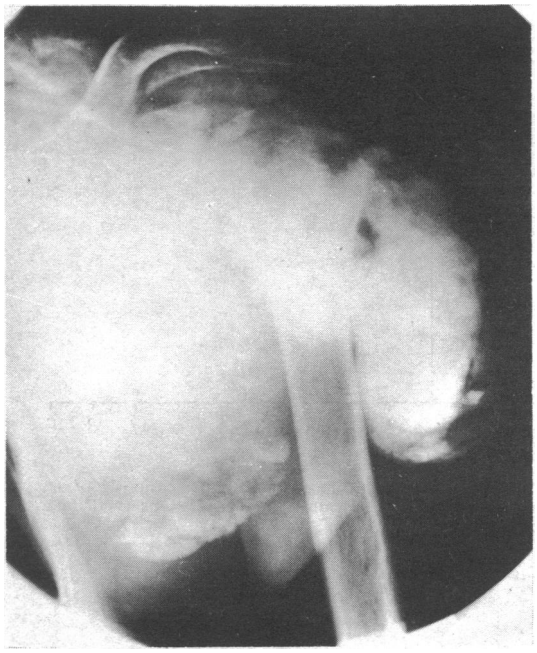

FIG. 6—Massive calcification around shoulder joint.

FRACTURES

Fractures and Looser zones were considered together since the latter were particularly difficult to identify with certainty. Altogether 32 patients had sustained a fracture at some time, and 25 of these had rib fractures which were often multiple. The next commonest sites of fracture were the bones of the hands and feet, suggesting a stress element. The $t_{\frac{1}{2}}$ for fractures was 9·1 years (fig. 4, table IV). The predialysis incidence of renal osteodystrophy was estimated by extrapolation of the computer-fitted curves (table IV).

Discussion

The population in this study was distributed through a wide age range. Though many more males than females had been dialysed for over four years the overall proportion of males to females was about 4:3. The radiographical features described cannot therefore be attributed to the preponderance of any particular group. By excluding the more subjective radiographic signs it was possible to obtain analysable data which were of some predictive value.

The radiographic lesions themselves—namely, erosions, ectopic calcification, and fractures—are well recognized. Vascular calcification was, surprisingly, found in 27% of the patients at the start of haemodialysis and rapidly increased with a $t_{\frac{1}{2}}$ of only 3·4 years. These results contrast with those of Curtis *et al.* (1969), who reported that metastatic calcification neither developed nor worsened after the start of maintenance haemodialysis therapy. Cohen *et al.* (1970) also found that this lesion remained static or progressed slowly in 8 out of 29 patients. Unfortunately there is no uniformity of criteria or technique in the three studies, so that comparisons may be misleading. The calcified ring or tube sign in the dorsalis pedis artery was of great diagnostic value (fig. 5). This appeared in early films as a hazy stippling, gradually progressing to complete ring formation. The sequential development will be described elsewhere (Tatler *et al.*, paper in preparation).

The initial incidence of fractures (7%) and erosions (12%) agrees with many previous reports stating that renal osteo-

dystrophy may reach an advanced stage long before terminal uraemia (Parsons, 1927; Liu and Chu, 1943). Erosions, however, were surprisingly late to develop, with a $t\frac{1}{2}$ of 22·9 years. The late appearance of the radiographic features of secondary hyperparathyroidism encourages a selective approach to parathyroidectomy. We are at present unable to say whether the gradual increase in dialysis fluid calcium concentration is responsible for the slow development of erosions, but this is being studied at present.

A factor which may be relevant is that only two of the patients had a bilateral nephrectomy. The retention of non-excretory renal tissue may allow varying dregees of vitamin D metabolism. Indeed the prolonged time course of several of the lesions studied (table IV), in particular subperiosteal erosions, provides some support for this hypothesis.

Fractures were often but not always related to stress and were not always painful. Looser zones were thought to be uncommon, in agreement with Ritz *et al.* (1971), who found this feature in only 1% of 282 patients.

Periarticular calcification was a common finding and did not appear to be related to the calcium phosphate product, though the average calcium concentration was raised, and the average serum phosphate for the group was 5 mg/100 ml (Varghese *et al.*, 1973). The soft-tissue calcification around the shoulder joint of one patient (fig. 6) resembled tumoral calcinosis (Slavin *et al.*, 1973); this degree of soft-tissue calcification was unusual.

This study emphasizes the importance of using objective radiographic signs and of undertaking regular radiographic reviews in dialysis patients. It also underlines the fact that though the disease is progressive the decline in normality for the group as a whole is slow, particularly for osteitis fibrosa ($t\frac{1}{2}$ 22·9 years). Vascular calcification, an important practical consideration where arteriovenous shunts or fistulae are required, develops rapidly and may indirectly influence patient survival, since blood access maintenance and renal transplantation are bound to be technically more hazardous in patients with heavily calcified vessels. It seems unlikely from the early high frequency of vascular calcification that it could be related to dialysis fluid calcium concentration; however, it is known that patients may gain a substantial amount of calcium from the dialysis solution (Wing, 1968). Parfitt *et al.* (1971) found that periarticular and arterial calcification worsened with a dialysis calcium concentration of $6{\cdot}87 \pm 0{\cdot}58$ mg/100 ml, a lower concentration than that which we now use.

At present there is no clear explanation for the differing rates of development of radiographic lesions shown in this study. Vascular calcification, the earliest to appear ($t\frac{1}{2}$ 3·4 years), may be a penalty for the suppression of parathyroid hormone activity which probably results from using high dialysate calcium in conjunction with oral aluminium hydroxide. On the other hand, the prolonged $t\frac{1}{2}$ for osteitis fibrosa (22·9 years) may reflect the response of the majority to this regimen, but emphasizes that a number of patients exist in whom suppression of the parathyroids with high dialysate calcium is not readily attained. This problem is undergoing more detailed study at the present time. All the lesions described occur in the absence of vitamin D metabolites, and it is clear that restoration of normality will not be achieved without a solution to this aspect of the disease.

Conclusions

We conclude that in this group of patients renal osteodystrophy has a prolonged time course. This could be due to partial ability to metabolize vitamin D, a gradual rise in dialysate calcium, or control of serum phosphate or a combination of all these. Evaluation of the time course will allow a rational approach to therapy in renal osteodystrophy. The simplicity of this method of using objective radiographical signs is emphasized, particularly as the radiographical findings correlate well with biochemical findings (Varghese *et al.*, 1973).

References

Baillod, R. A., Crockett, R. E., and Ross, A. (1969). *Proceedings of the European Dialysis and Transplant Association*, **5**, 97.

Baillod, R. A., Ku, G., and Moorhead, J. F. (1972). *Proceedings of the European Dialysis and Transplant Association*, **10**, 335.

Cohen, M. E. L., Cohen, G. F., Amad, V., and Kaye, M. (1970). *Clinical Radiology*, **21**, 124.

Craswell, P. W., *et al.* (1972). *British Medical Journal*, **4**, 749.

Curtis, J. R., *et al.*, (1969). *Quarterly Journal of Medicine*, **38**, 49.

Dick, R., and Jones, D. N. (1973). *Clinical Radiology*, **24**, 72.

Doyle, F. H. (1972). *British Medical Bulletin*, **28**, 220.

Ginzler, A. M., and Jaffe, H. L. (1941). *American Journal of Pathology*, **17**, 293.

Liu, S. H., and Chu, H. I. (1943). *Medicine*, **22**, 103.

Lucas, R. C. (1883). *Lancet*, **1**, 993.

MacCallum, W. G. (1905). *Johns Hopkins Hospital Bulletin*, **166**, 87.

Moorhead, J. F., Baillod, R. A., and Hopewell, J. P. (1970). In *Proceedings of 4th International Congress of Nephrology*, ed. N. Alwall, F. Berglund, and B. Josephson, vol. 3, p. 131. New York, Karger.

O'Riordan, J. L. H., *et al.* (1970). *Quarterly Journal of Medicine*, **39**, 359.

Parfitt, A. M., Massry, S. G., Wingfield, A. G., DePalma, J. R., and Gordon, A. (1971). *American Journal of Medicine*, **51**, 319.

Parsons, L. G. (1927). *Archives of Disease in Childhood*, **2**, 1.

Pendras, J. P., and Erickson, R. V. (1966). *Annals of Internal Medicine*, **64**, 276.

Ritz, E., *et al.* (1971). *Proceedings of the European Dialysis and Transplant Association*, **8**, 131.

Siddiqui, J., and Kerr, D. N. S. (1971). *British Medical Bulletin*, **27**, 153.

Slavin, G., Klenerman, L., Darby, A., and Bansal, S. (1973). *British Medical Journal*, **1**, 147.

Varghese, Z., Moorhead, J. F., Tatler, G. L. V., Baillod, R. A., and Wills, M. R. (1973). *Proceedings of the European Dialysis and Transplant Association*, **10**, 187.

Virchow, R. (1855). *Archiv fur Pathologische Anatomie und Physiologie und fur Klinische Medizin*, **8**, 103.

Wing, A. J. (1968). *British Medical Journal*, **4**, 145.