other agents. Various drug combinations, which include bleomycin, are currently being assessed, especially in the management of the lymphomas, and a second Medical Research Council trial to compare bleomycin and radiotherapy with radiotherapy alone for moderately advanced squamous cell carcinoma of mouth, pharynx, larynx, and oesophagus continues (further participation in this trial would be welcomed).

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References

[1] Halnan, K E, *et al*, *British Medical Journal*, 1972, **4**, 635.
[2] Peto, R, *Applied Statistics*, 1973, **22**, 86.
[3] de Palo, G M, *et al*, *Cancer Chemotherapy Reports*, 1973, **57**, 429.

Barbiturate and anticonvulsant treatment in relation to osteomalacia with haemodialysis and renal transplantation

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Summary

Among 39 patients treated by regular haemodialysis for four years or more pathological fractures and histological evidence of osteomalacia were significantly more common in those taking barbiturates. Out of 58 transplant recipients surveyed after one year, seven had osteomalacia; four of these had been taking phenobarbitone and phenytoin and one had taken barbiturates alone. Sedatives and other drugs such as phenobarbitone and phenytoin that induce hepatic microsomal enzymes should probably be avoided when possible in patients with chronic renal failure and after transplantation.

Introduction

Patients on regular haemodialysis at Newcastle upon Tyne have a high incidence of osteomalacia, which is characterised by bone pain, pathological fractures, myopathy, and reduced physical activity.[1 2] Comparison with another British centre confirmed this but showed no obvious differences in dialysis technique.[3] Drug treatment, other than with heparin, vitamin D, calcium supplements, and phosphate binders was not taken into consideration. During the 1960s barbiturates were given regularly at night to patients on dialysis and some of the long-term survivors continued to take them until recently. Prolonged anticonvulsant treatment was given to patients who had convulsions early in the course of their management. Because of the association between anticonvulsants and osteomalacia in epilepsy[4 5] we decided to review the drug treatment of all the patients who had at any time completed not less than four years on regular haemodialysis at Newcastle and to relate it to the incidence of osteomalacia in these patients.

Renal osteodystrophy resolves rapidly after successful renal transplantation.[6 7] The different histological components resolve at different rates, but osteomalacia usually heals promptly. In 81% of our patients with histological evidence of osteomalacia at the time of transplantation the changes had completely resolved a year later.[7] Surprisingly, however, in a few patients with adequate renal function osteomalacia progressed or developed afresh after successful transplantation. Review of these patients showed that many had been treated with anticonvulsants or sedatives for long periods after transplantation.

Patients and methods

Bone histopathology had been studied in serial transiliac bone biopsies. Osteomalacia was diagnosed only when there was an excess of osteoid, with abnormally thick osteoid seams comprising five or more birefringent lamellae, and a reduced or absent calcification front.[8] Radiological skeletal surveys had been carried out at six-monthly intervals. Serum calcium had been measured by atomic absorption spectrophotometry,[9] and all values corrected to a total serum protein level of 72 g/l. Serum alkaline phosphatase had been measured by a modification of the method of Bowers and McComb.[10]

Thirty-nine patients had completed four or more years of regular haemodialysis. Some of them had subsequently been transplanted or died. Complete records of drug treatment were available from their dialysis sheets. Questionnaires on symptoms and records of physical examination had been completed at six-monthly follow-up visits, from which we assessed the degree of bone pain, muscle weakness, and physical activity.

Fifty-eight transplant recipients followed up in the transplant clinic had had a full reassessment of bone status at one year. Their drug treatment was also reviewed. Seven (12%) had had histological evidence of osteomalacia, and of these 5 (71%) had received prolonged treatment with enzyme-inducing drugs. The case histories of these five patients are given below.

CASE 1

A 30-year-old woman received a cadaveric renal transplant on 20 March 1972, three years after beginning regular haemodialysis. After about nine months of regular haemodialysis she had developed symptomatic bone disease, which progressed to pronounced weakness of her quadriceps and difficulty with walking. Osteomalacia was confirmed by transiliac bone biopsy after 14, 27, and 36 months of regular haemodialysis, but no evidence of osteitis fibrosa was found. There was a progressive loss of total and mineralised

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bone and an increasing thickness of patchily distributed osteoid seams. The bone biopsy specimen taken at 36 months, on the day of transplantation, showed: total bone (TB) 14·1% mineralised bone (MB) 13·3%, osteoid (O) 0·8%, cancellous bone 94·7% mineralised, calcification front (CF) reduced, maximum number of birefringent osteoid lamellae (OL) 6. During the period on haemodialysis she had received phenytoin, Mandrax, (methaqualone and diphenhydramine hydrochloride), and amylobarbitone.

After transplantation regular treatment with amylobarbitone was continued until March 1973, when the patient was admitted as an emergency case after having taken an overdose of these tablets. Barbiturates were withdrawn.

Despite the restoration of adequate renal function (table I) her symptomatic bone disease did not improve. One year after transplantation there was biochemical (table I), radiological (fig 1), and histological evidence of osteomalacia. For the first time there was a moderately severe degree of osteitis fibrosa (grade 2·5). The increased osteoblastic activity associated with this may have contributed to the further increase in osteoid (TB 23·9%, MB 19·8%, O 4·1%, cancellous bone 82·9% mineralised, CF reduced, OL 5). She was started on calciferol 50 000 units daily at the same time as the barbiturates were stopped, and from then onwards she steadily improved. A further bone biopsy a year later showed resolution of the osteomalacia with only a little excess osteoid attributable to mild continued osteitis fibrosa (grade 1). Her total bone mass was again reduced and the cancellous bone trabecular pattern was abnormal as a result of previous resorption (TB 16·5%, MB 15·1%, O 1·4%, cancellous bone 91·4% mineralised, CF normal. OL 3).

Serial skeletal surveys during regular haemodialysis showed unhealed rib fractures. Twelve months after transplantation the patient had Looser's zones in the pubic rami (fig 1) and ribs. After a year on calciferol the Looser zones in the pubic rami healed.

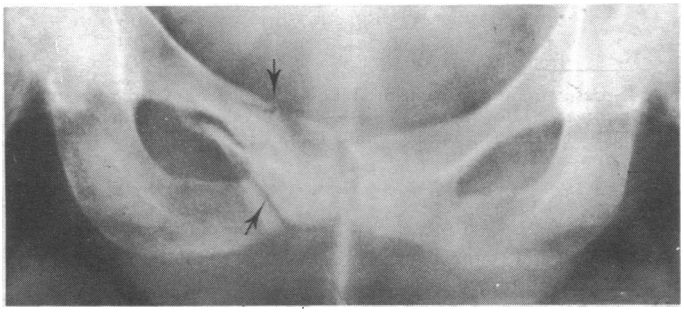

FIG 1—Case 1. *X*-ray film of pubic rami showing Looser's zones (arrowed).

CASE 2

A 38-year-old man received a successful renal transplant on 20 November 1973 after two uneventful months on regular haemodialysis. Bone biopsy on the day of the operation showed mild osteitis fibrosa (grade 1·5) but no osteomalacia (TB 17·3%, MB 16·8%, O 0·5%, cancellous bone 97·1% mineralised, CF normal, OL 3). Five weeks later he had a series of generalised convulsions. Thrice-daily phenobarbitone 60 mg and phenytoin 100 mg was begun and continued for the next 13 months. Bone biopsy 12 months after transplantation showed mild osteitis fibrosa (grade 1) and moderate osteomalacia (TB 28·3%, MB 25·5%, O 2·8%, cancellous bone 90·2% mineralised, CF reduced, OL 9). He complained of musculoskeletal aches and pains, had a raised serum alkaline phosphatase level, but showed no fractures or Looser's zones on a skeletal survey.

CASE 3

A 57-year-old man received a successful renal transplant on 14 January 1974. In October 1972 he had begun regular haemodialysis and bone biopsy had shown mild osteitis fibrosa (grade 1·5) but no osteomalacia (TB 19·6%, MB 18·9%, O 0·7%, cancellous bone 96·5% mineralised, CF normal, OL 3). The slight excess of osteoid was attributed to the osteitis fibrosa. Aluminium hydroxide 20 ml four times a day produced a moderate hypophosphataemia. By April 1973 he had developed symptomatic bone disease and proximal myopathy confirmed by electromyography. Bone biopsy in May 1973 showed a reduction in the severity of osteitis fibrosa (grade 1) but mild osteomalacia had developed (TB 23·7%, MB 22·0%, O 1·7%, cancellous bone 92·9% mineralised, CF reduced, OL 6). Also in May 1973 he had a series of convulsions and began thrice-daily phenobarbitone 30 mg and phenytoin 100 mg, which was continued unchanged.

Despite a successful renal transplant, bone biopsy five months after the operation showed more-severe osteomalacia (TB 18·2%, MB 15·5%, O 2·7%, cancellous bone 85·1% mineralised, CF reduced, OL 7) but no definite evidence of osteitis fibrosa. Osteomalacia was still present 12 months after transplantation (TB 28·1%, MB 23·7%, O 4·4%, cancellous bone 84·5% mineralised, OL 7). There was then also recognisable mild osteitis fibrosa (grade 1·5). An attempt to discontinue anticonvulsant treatment resulted in another seizure. At the time of writing he was continuing with the anticonvulsants and receiving 50 000 units calciferol daily by mouth. Skeletal surveys six and 12 months postoperatively showed rib fractures with features suggesting Looser's zones.

CASE 4

A 53-year-old woman received a successful renal transplant on 19 July 1972 after four years on regular haemodialysis. Bone biopsy 13 months before haemodialysis began showed mild osteitis fibrosa (grade 1·5) and moderately severe osteomalacia (TB 22·3%, MB 15·6%, O 5·7%, cancellous bone 70·0% mineralised, CF reduced, OL 8). Bone disease persisted, and after 33 months of haemodialysis bone biopsy showed slightly more-severe osteitis fibrosa (grade 2) and continued osteomalacia (O 4·8%, cancellous bone 84·1% mineralised, CF reduced, OL 6).

Two weeks after transplantation the patient had a series of generalised convulsions and began treatment with phenobarbitone and phenytoin. After three months the dosage was gradually reduced, but within two months she was readmitted with further convulsions. Anticonvulsant treatment was reinstituted, and long-term treatment with phenytoin 100 mg three times a day was being maintained at the time of writing. Bone biopsy 12 months after transplantation showed increased osteitis fibrosa (grade 2·5) and continued osteomalacia (TB 25·4%, MB 24·2%, O 1·2%, cancellous bone 95·0% mineralised). With 50 000 units calciferol daily by mouth her symptomatic bone disease improved, and bone biopsy two years after transplantation confirmed complete resolution of the osteomalacia, though bone was much reduced (TB 8·7%, MB 8·4%, O 0·3%, cancellous bone 96·0% mineralised, CF normal, OL 3). There was still a mild degree (grade 1) of osteitis fibrosa. During regular haemodialysis serial skeletal surveys had shown several metatarsal fractures and also fractures of the distal ends of both ulnae. These developed callus, which was clearly recognisable 12 months postoperatively. After calciferol there was evidence of remodelling.

CASE 5

A 24-year-old woman received a successful renal transplant on 30 April 1968 after three years on regular haemodialysis. During this period she had infrequent convulsions and was given phenobarbitone and phenytoin. This was continued after transplantation. During her three years on haemodialysis she developed symptomatic bone disease. Bone biopsy on the day of transplantation showed mild osteitis fibrosa (grade 1·5) with irregular thinning of the mineralised parts of the trabeculae and excess surface osteoid with osteomalacia (TB 19·3%, MB 17·8%, O 1·5%, cancellous bone 92·6% mineralised, CF reduced, OL 6). Postoperatively her musculoskeletal complaints increased and reached a peak in January 1971, when she was noted to have a grossly myopathic and waddling gait. Radiography showed extensive pseudofractures in both femoral necks and feet, as well as elsewhere (figs 2 and 3).

TABLE I—*Biochemical values, histological data, and treatment in the five patients with post-transplant osteomalacia*

Case No	Date of observation after transplantation	Serum creatinine (μmol/l)	Serum calcium (mmol/l)	Serum phosphate (mmol/l)	Alkaline phosphatase (U/l)	Histological osteomalacia	Azathioprine (mg/day)	Prednisone (mg/day)
1	1 year	168	2·32	1·45	288	Yes	150	20·0
	2 years	243	2·35	1·19	76	No	100	15·0
2	1 year	97	2·55	0·67	156	Yes	200	12·5
3	1 year	106	2·40	0·87	222	Yes	50	12·5
4	1 year	221	2·35	1·54	152	Yes	50	22·5
	2 years	164	2·42	1·09	73	No	50	10·0
5	2 years 8 months	66	2·27	0·74	741	*	50	
	4 years	106	2·52	1·22	68	No	50	

*Biopsy not done.
Conversion: SI to traditional units—Serum creatinine: 1 μmol/l ≈ 0·0113 mg/100 ml. Serum calcium: 1 mmol/l ≈ 4·0 mg/100 ml. Serum phosphate: 1 mmol/l ≈ 3·1 mg/100ml

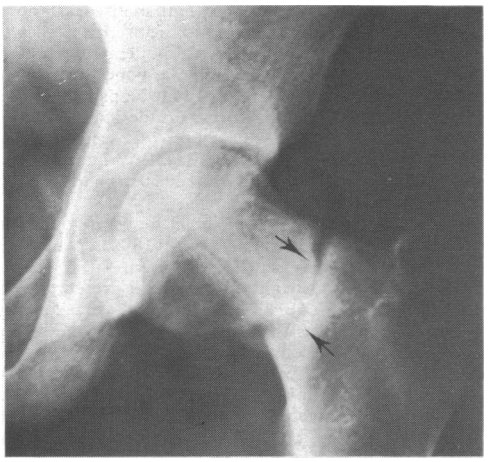

FIG 2—Case 5. *X*-ray film of left femoral neck showing Looser's zones (arrowed).

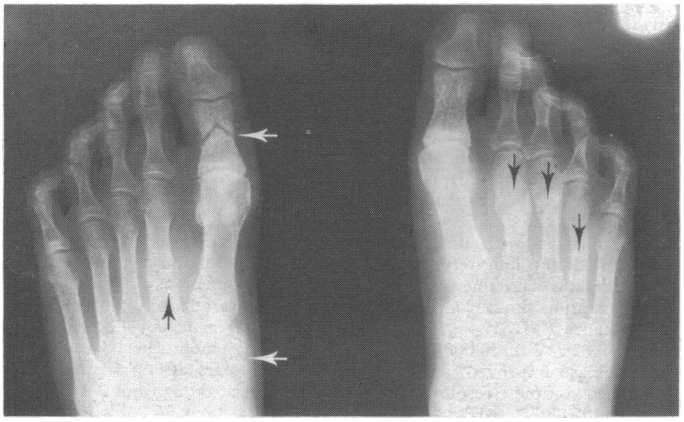

FIG 3—Case 5. Appearances of Looser's zones (arrowed) in feet.

Results

Of the 39 patients who completed four years on regular haemodialysis 23 had received barbiturates for six months or more as either anticonvulsants or hypnotics and 16 had taken no nocturnal sedatives or had received nitrazepam alone; in non-uraemic people nitrazepam does not induce hepatic microsomal enzymes.[11] Signs of hyperparathyroidism such as subperiosteal erosions in the hands did not differ significantly in the two groups. Those taking barbiturates had more bone pain and myopathy and were less physically active, but the differences were not significant at the 5% level. They had, however, significantly more pathological fractures and a greater incidence of histological osteomalacia (table II).

In four of the five patients described above osteomalacia had been present at the time of transplantation, but they differed from most patients with this lesion in that it failed to heal spontaneously by the end of the first year. In case 2 osteomalacia appeared as a new finding after transplantation. Restoration of renal function was adequate in all five patients (table I); three had a serum creatinine concentration below 132 μmol/l (1·5 mg/100 ml), and the other two had serum creatinine levels between 132 and 265 μmol/l. A rise in serum alkaline phosphatase was a reliable guide to the presence of osteomalacia in these patients, especially when the enzyme was shown by isoenzyme studies to be derived mainly from bone. With calciferol treatment the serum alkaline phosphatase fell slowly to normal (fig 4; cases 1, 4, and 5).

Radiological evidence of osteomalacia with pseudofractures appeared in four of these five patients; usual sites were the ribs, metatarsals, pubic rami, and femoral necks (figs 1-3).

TABLE II—*Results of correlation analysis between drug treatment and presence of osteomalacia histologically and radiological evidence of fractures in patients on regular haemodialysis*

	Histological osteomalacia		Fractures	
	Absent	Present	Fewer than four ribs and no other sites	More than four ribs and other sites
Non-hepatic microsomal enzyme-inducing drugs (nitrazepam)	7	5	11	5
Hepatic microsomal enzyme-inducing drugs (barbiturates)	2	15	7	16
Fisher's exact test	P<0·05		P<0·05	

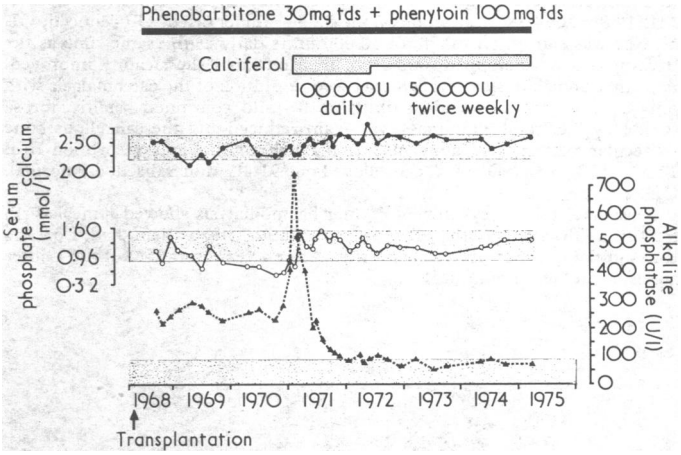

FIG 4—Case 5. Serial biochemical findings related to drug treatment. *Conversion: SI to traditional units*—Serum calcium: 1 mmol/l ≈ 4·0 mg/100 ml. Serum phosphate: 1 mmol/l ≈ 3·1 mg/100 ml.

Discussion

These results suggest that in patients on regular haemodialysis in Newcastle upon Tyne hepatic microsomal enzyme-inducing drugs such as barbiturates and phenytoin are related to the osteomalacic component of renal osteodystrophy. Since several patients not on such drugs also develop this complication enzyme-inducing drugs cannot be the whole explanation of symptomatic bone disease but their use clearly aggravates the tendency towards uraemic osteomalacia. Another cause of haemodialysis osteomalacia is treatment with excessive amounts of phosphate binders,[12] as illustrated by one of our patients (case 3), whose onset of myopathy and osteomalacia coincided with the introduction of phosphate binders and a hypophosphataemia to 0·5 mmol/l (1·5 mg/100 ml). So far as we know barbiturates have not previously been incriminated as a cause of symptomatic bone disease in dialysed patients.

A similar adverse effect of enzyme-inducing drugs on bone mineralisation was also noted after successful renal transplantation in five out of seven patients, in whom osteomalacia was clearly related to prolonged treatment with phenytoin and barbiturates. Investigations failed to show any other cause. Thus anticonvulsant treatment appeared to be the commonest cause of osteomalacia after transplantation in our series. Four patients received a combination of barbiturates and phenytoin and one received barbiturates alone. In each case the treatment was prolonged. Three other transplant recipients had received known enzyme-inducing drugs, but they did not have osteomalacia at the end of the first transplant year. One of the three had received anticonvulsant treatment only for the first four postoperative months. Another had taken phenobarbitone 30 mg twice daily, and the third had taken phenytoin 100 mg twice daily intermittently.

Probably, therefore, in transplant recipients, as in normal, non-uraemic people, such drugs do not always cause osteomalacia, but when treatment is prolonged the incidence of osteomalacia is increased. Why transplanted patients with normal or nearly normal renal function are so sensitive to

anticonvulsants and barbiturates is uncertain. Possibly a skeleton damaged by pretransplant uraemia is unusually susceptible to changes in vitamin D metabolism, and changes in liver function produced by immunosuppressive drugs may play a part.

In non-uraemic epileptic patients treated with phenobarbitone and phenytoin there is an increased turnover of 25-hydroxycholecalciferol with the production of more polar, biologically inactive metabolites that are excreted in the bile at an accelerated rate.[13 14] This is attributed to drug-induced enhancement of hepatic microsomal enzyme activity.[13-15] A similar increased turnover of vitamin D occurs in uraemia.[16] This may well result from an increase in hepatic microsomal activity, which has been found in uraemic patients.[17] Wake and Maddocks[17] have also shown that in uraemic patients hepatic enzymes may be further induced by phenobarbitone by mouth, so that it would not be surprising if anticonvulsants accentuated this abnormality of vitamin D metabolism. In 1974 we suggested a possible aetiological role for enzyme-inducing drugs in the osteomalacia of transplanted patients.[7] This form of osteomalacia is to some extent resistant to vitamin D. In three of the cases reported here large doses of calciferol (50 000 units daily) were required to effect recovery.

Awareness of the risk of osteomalacia when enzyme-inducing drugs such as phenytoin and phenobarbitone are given in uraemia and after renal transplantation should lead to more cautious use of these drugs and their earlier withdrawal. When their continued use is essential in patients who have had transplants prophylactic treatment with large vitamin D supplements is probably advisable. We have not succeeded in healing osteomalacia in patients on regular dialysis taking enzyme-inducing drugs with calciferol and dihydrotachysterol, and their condition is also relatively resistant to 1-alpha-hydroxycholecalciferol. Consequently sedatives and other drugs known to induce hepatic enzymes should be avoided so far as possible during regular haemodialysis.

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References

1 Siddiqui, J, and Kerr, D N S, *British Medical Bulletin*, 1971, **27**, 153.
2 Simpson, W, *et al*, *British Journal of Radiology*, In press.
3 Siddiqui, J, *et al*, *Proceedings of the European Dialysis and Transplant Association*, 1971, **8**, 149.
4 Dent, C E, *et al*, *British Medical Journal*, 1970, **4**, 69.
5 Richens, A, and Rowe, D J F, *British Medical Journal*, 1970, **4**, 73.
6 Carroll, R N P, *et al*, *Proceedings of the European Diaylsis and Transplant Association*, 1973, **10**, 446.
7 Pierides, A M, *et al*, *Proceedings of the European Dialysis and Transplant Association*, 1974, **11**, 481.
8 Ellis, H A, and Peart, K M, *Journal of Clinical Pathology*, 1973, **26**, 83.
9 Willis, J B, *Spectrochimica Acta*, 1960, **16**, 259.
10 Bowers, N G, and McComb, R B, *Clinical Chemistry*, 1966, **12**, 1970.
11 Whitfield, J B, *et al*, *British Medical Journal*, 1973, **1**, 316.
12 Hill, A V L, *et al*, in *Proceedings of Second Workshop on Vitamin D, Wiesbaden*, 1974, ed A W Norman, *et al*, p 643. New York, de Gruyter, 1975.
13 Hahn, T J, *et al*, *Journal of Clinical Investigation*, 1972, **51**, 741.
14 Jubiz, W, *et al*, *New England Journal of Medicine*, 1970, **283**, 11.
15 Hunter, J, *et al*, *British Medical Journal*, 1971, **4**, 202.
16 Avioli, L V, *et al*, *Journal of Clinical Investigation*, 1968, **47**, 2239.
17 Wake, C J, and Maddocks, J L, *Lancet*, 1975, **1**, 516.

Plasma prednisolone levels after administration of prednisolone-21-phosphate as a retention enema in colitis

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Summary

A competitive protein-binding assay was used to measure plasma prednisolone levels after administration of prednisolone-21-phosphate retention enemas to seven patients with colitis. Prednisolone appeared in the plasma of all patients after the enema, and concentrations rose to a peak within three hours. In five of the patients plasma prednisolone levels were also measured after the same dose of prednisolone by mouth. Although in individual patients the plasma levels achieved by enema were often quite different from those achieved by mouth, overall the levels achieved by each mode of administration were of a similar order. These findings suggest that 20 mg prednisolone given by retention enema may well exert a systemic effect.

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Introduction

Prednisolone-21-phosphate administered as a retention enema is valuable in treating colitis[1] but there is doubt about how much prednisolone is absorbed from such enemas. Since it has hitherto been impossible to measure small quantities of prednisolone in blood samples observations on the absorption of prednisolone from the rectum have been indirect. Recent advances in the measurement of prednisolone by competitive protein binding[2] and by radioimmunoassay[3] have allowed nanogram quantities of the steroid to be measured directly in plasma. We describe here the use of a competitive protein-binding method to measure the amount of prednisolone absorbed from the rectum. We compared the levels observed after an oral dose of prednisolone with those after an equivalent dose given by retention enema in the same patient.

Patients and methods

Prednisolone was measured in 2-ml plasma samples using a competitive protein-binding assay[2] modified as described by Wilson