

# Renal osteodystrophy in nondialysed adolescents

## Long-term treatment with $1\alpha$ -hydroxycholecalciferol

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**SUMMARY** The effects of small oral doses (1-2  $\mu\text{g/day}$ ) of  $1\alpha$ -hydroxycholecalciferol, given for 1 to 2 years, have been examined in four nondialysed adolescents with chronic renal failure and bone disease. Treatment increased calcium retention and plasma calcium, and decreased plasma levels of alkaline phosphatase, hydroxyproline, and immunoreactive parathyroid hormone. X-ray abnormalities of bone regressed, and 2 patients underwent successful surgical correction of knock-knees; bone histology in these 2 was normal at the time of operation. 2 patients developed hypercalcaemia which promptly reversed when  $1\alpha$ -hydroxycholecalciferol was withdrawn. In one patient treatment was initially successful, but later there was biochemical, radiographic, and histological evidence of relapse. Long-term treatment of such patients with  $1\alpha$ -hydroxycholecalciferol may be effective and facilitate the surgical correction of deformities, but this is not invariable. Toxic effects are similar to those of vitamin D itself, but are more readily reversible.

Since the discovery that the kidney synthesizes  $1,25$ -dihydroxycholecalciferol ( $1\alpha,25$ -DHCC), which may be the major active metabolite of vitamin D (Holick and DeLuca, 1974; Kodicek, 1974), there has been considerable interest in its clinical application to the disorders of bone found in chronic renal failure. The development of bone disease and the resistance of such patients to treatment with vitamin D itself may result from impaired endogenous conversion of cholecalciferol to  $1\alpha,25$ -DHCC, due perhaps in part to a loss of renal tissue, and in part to hyperphosphataemia. Hence the administration of  $1\alpha,25$ -DHCC or its more readily synthesized analogue  $1\alpha$ -hydroxycholecalciferol ( $1\alpha$ -HCC) in physiological doses might be expected to reverse some of the abnormalities seen in bone. The immediate biological effects of these compounds in renal bone disease have encouraged their long-term evaluation. We report the effects of  $1\alpha$ -HCC given for up to 2 years in 4 nondialysed adolescents.

### Patients and methods

Four nondialysed adolescents with chronic renal failure and severe renal osteodystrophy were studied (Table). 3 of them had not taken vitamin D,

its metabolites or analogues for at least 1 year previously. One patient (Case 3, Table) had been treated with  $1\alpha,25$ -DHCC 0.7-1.35  $\mu\text{g}$  daily for the 5 months before this study (Henderson *et al.*, 1974, Case 4). Other drugs (Table) prescribed for each patient were continued unaltered throughout the investigation with the exception of Case 1, who was given propranolol for hypertension 6 months after the start of treatment. Each patient was initially treated with oral  $1\alpha$ -HCC 2  $\mu\text{g}$  daily. Thereafter the dose was altered from time to time (Figs. 2, 4, 7, 10).

Plasma calcium, inorganic phosphate, creatinine, nonprotein-bound hydroxyproline, and alkaline phosphatase were measured by standard techniques (Smith *et al.*, 1973). Normal adult ranges are shown in the Table. Renal tubular phosphate reabsorption, TmP/GFR, was estimated indirectly from fasting plasma and urine samples (Walton and Bijvoet, 1975). Metabolic balances of calcium and inorganic phosphate were measured in 2 patients using copper thiocyanate and carmine red as internal and external markers respectively. Samples of diet were regularly analysed. Plasma immunoreactive parathyroid hormone (iPTH) was measured by radioimmunoassay (Berson *et al.*, 1963) using an antibody (coded 211:32, Wellcome Laboratories Ltd.) reacting preferentially but not exclusively

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Table Clinical and biochemical details of 4 adolescents before treatment with 1 $\alpha$ -HCC

Clinical details									
Case no.	Age (years)	Sex	Height (cm)	Weight (kg)	Renal disease	Radiological findings	Bone biopsy	Symptoms & signs	Concurrent medication
1	17	M	156	41.8	Mesangio-capillary glomerulonephritis	Marked clavicular and phalangeal subperiosteal erosions hyperparathyroid changes (Fig. 6)	Osteodystrophy	Knock knees	Methyldopa, propranolol, aluminium hydroxide Sodium supplements
2	14	M	122	21.0	Obstructive uropathy	Severe and widespread changes (Fig. 6)	—	Dwarfism; severe skeletal deformity	Sodium supplements
3	16	F	150	53.5	Interstitial nephritis	Severe rickets genu valgum, subperiosteal erosions of phalanges	Osteomalacia*	Skeletal pain on exercise; knock knees	Sodium potassium, and iron supplements
4	13	F	147	49.5	Obstructive uropathy	Severe rickets (Fig. 8)	—	Knock knees	Sodium and iron supplements

Mean plasma values in month preceding treatment†					
Calcium (mmol/l) (2.12–2.65)	Inorganic phosphate (mmol/l) (0.94–1.55)	Alkaline phosphatase (IU/l) (35–80)	Plasma hydroxyproline ( $\mu$ mol/l) (2–19)	iPTH ( $\mu$ g/l) (<0.5)	Creatinine ( $\mu$ mol/l) (70–150)
2.23	3.15	382	163	4.3	480
2.40	2.61	544	441	23.0	640
2.32*	1.75*	300*	87*	9.5*	570*
1.78	1.55	628	52	1.8	450

\* Bone biopsy was performed before treatment with 1 $\alpha$ , 25-DHCC (see Methods) and biochemical data given are those before the 2nd course of treatment with 1 $\alpha$ -HCC (see Fig. 7).

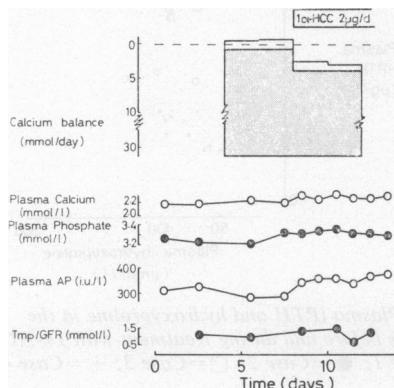
† Normal adult ranges of the biochemical determinations are given in parentheses.

Conversion: SI to traditional units—Calcium: 1 mmol/l  $\approx$  4 mg/100 ml. Phosphate: 1 mmol/l  $\approx$  3.1 mg/100 ml. Creatinine: 1  $\mu$ mol/l  $\approx$  0.01 mg/100 ml. Hydroxyproline: 1  $\mu$ mol/l  $\approx$  0.13 mg/l.

to the amino-terminal portion of PTH. Intestinal absorption of calcium was assessed in one patient using a total body counter by the 7-day retention of an oral dose of 2–6  $\mu\text{Ci}$   $^{47}\text{Ca}$  given in 200 mg of calcium as gluconate (Henderson *et al.*, 1974). Iliac bone biopsy, under local anaesthesia, was performed in 2 patients.

## Results

**Case 1.** During the first 4 days of treatment calcium balance became positive (Fig. 1) with little

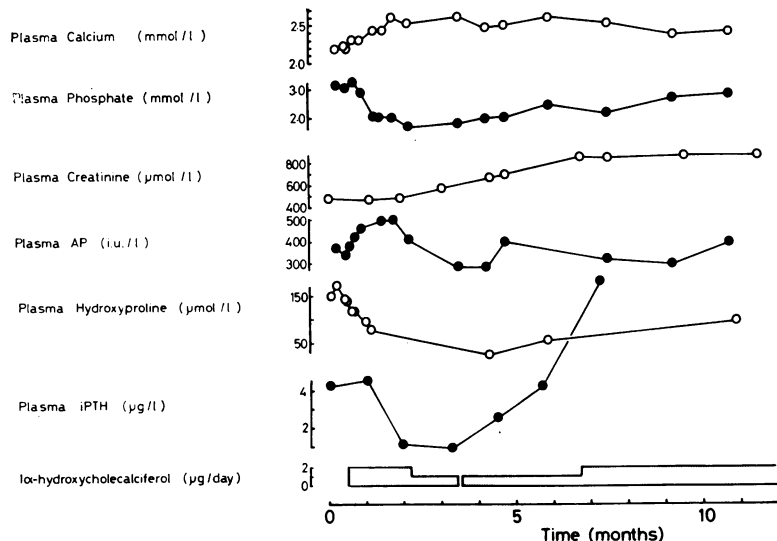


**Fig. 1** Case 1. The initial effect of 1 $\alpha$ -hydroxycholecalciferol (1 $\alpha$ -HCC). In the metabolic balance, intake is plotted down from zero line, and faecal (shaded) and urine (clear) excretion is plotted upwards from the foot of the intake line. AP=alkaline phosphatase; Tmp/GFR=renal tubular phosphate reabsorption. For conversion from SI to traditional units for calcium and phosphate, see footnote to Table.

corresponding change in phosphate balance (+10.8 to +11.5 mmol/24 h; +0.33 to +0.36 g/24 h). Improvement in calcium balance was largely due to increased net intestinal absorption, but there was also a detectable fall in urinary calcium despite an increase in plasma calcium and with no change in plasma creatinine.

During long-term treatment (Fig. 2) plasma creatinine slowly increased. Plasma calcium and alkaline phosphatase rose, while plasma phosphate fell with no apparent changes in diet or dose of phosphate binding agents. Plasma iPTH fell when the plasma calcium rose. After 2½ months plasma alkaline phosphatase began to fall. The dose of 1 $\alpha$ -HCC was reduced to 1  $\mu\text{g}$  daily when plasma calcium exceeded 2.6 mmol/l (10.4 mg/100 ml). On this reduced dose plasma levels of iPTH, hydroxyproline, and alkaline phosphatase remained low for a further 2 months suggesting that treatment was adequate. After 5 months subperiosteal erosions healed. However, thereafter plasma iPTH, hydroxyproline, and alkaline phosphatase activity increased despite continuing treatment with 1 $\alpha$ -HCC now in a daily dose of 2  $\mu\text{g}$ . This 'breakthrough' phenomenon on doses of 1 $\alpha$ -HCC found to be previously effective, was accompanied by a recurrence of subperiosteal bone erosions and progression of knock-knee deformity. Bone biopsy after 10 months showed no change in the florid osteitis fibrosa with osteomalacia seen before treatment. The rates of change of height and weight were unaffected by treatment.

**Case 2.** This boy's renal function remained stable throughout the study (Table). Calcium and



**Fig. 2** Case 1. The long-term biochemical effects of continuous treatment with 1 $\alpha$ -HCC. For conversion from SI to traditional units, see footnote to Table.

phosphate balances were consistently negative (Fig. 3 shows one of 3 pretreatment balances) and  $^{47}\text{Ca}$  absorption 33%. After 18 months of  $1\alpha\text{-HCC}$ , calcium and phosphate balances were markedly positive and  $^{47}\text{Ca}$  absorption had increased to 72%. There were no changes in magnesium balance. As in Case 1 (Fig. 1) the change in calcium balance was due mainly to an increase in net absorption, but the urinary excretion rate of calcium had also decreased, even though there was no fall of plasma calcium.

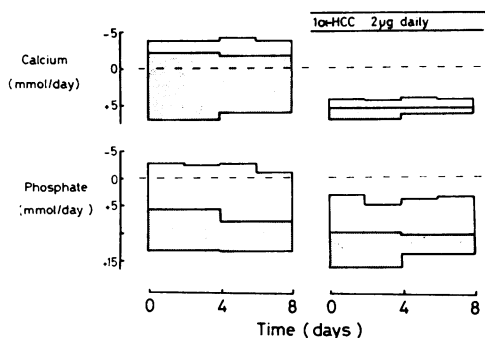


Fig. 3 Case 2. Metabolic balances before  $1\alpha\text{-HCC}$  (left), and after 18 months of treatment with  $1\alpha\text{-HCC}$  (right). This small patient (Table) normally ate very little calcium. Balances are plotted as Fig. 1.

In the first 9 months of treatment (Fig. 4) there was a fall in plasma alkaline phosphatase, plasma iPTH, and hydroxyproline, which continued when the daily dose of  $1\alpha\text{-HCC}$  was reduced to  $1\ \mu\text{g}$ . After 11 months of continuous treatment  $1\alpha\text{-HCC}$  was stopped because of hypercalcaemia (calcium  $>2.65\ \text{mmol/l}$ ;  $>10.6\ \text{mg/100 ml}$ ), and plasma

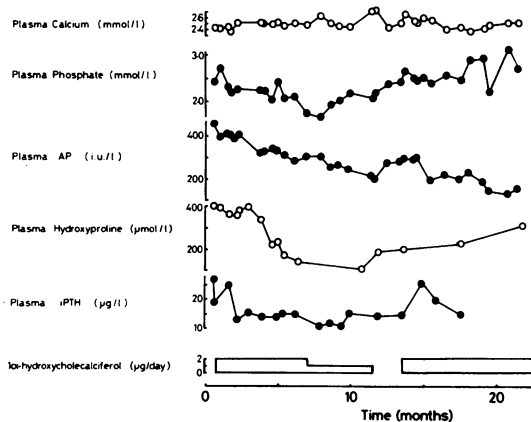


Fig. 4 Case 2. Long-term biochemical responses to treatment with  $1\alpha\text{-HCC}$ .

hydroxyproline and alkaline phosphatase began to rise. When treatment was restarted, plasma alkaline phosphatase fell, but the earlier fall in plasma hydroxyproline was not observed and levels rose despite continued treatment. There was a positive correlation of plasma iPTH with plasma hydroxyproline throughout the period of study ( $r = +0.80$ ;  $P < 0.02$ , Fig. 5).

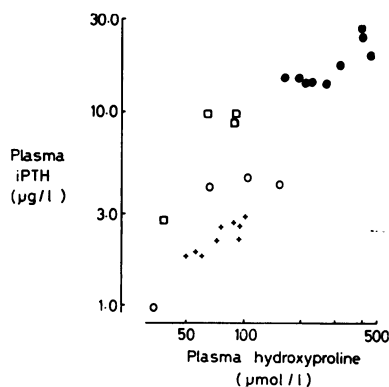


Fig. 5 Plasma iPTH and hydroxyproline in the 4 patients before and during treatment with  $1\alpha\text{-HCC}$ .  $\circ$  = Case 1;  $\bullet$  = Case 2;  $\square$  = Case 3;  $+$  = Case 4.

During treatment skeletal x-rays showed healing of bone resorption though skeletal deformities persisted (Fig. 6).

**Case 3.** This patient had been treated previously with  $1\alpha,25\text{-DHCC}$  ( $0.67\text{--}1.35\ \mu\text{g}$  daily for 5 months). The pain in her knees had improved and radiological resolution of rickets and subperiosteal erosions had occurred (Henderson *et al.*, 1974). Plasma alkaline phosphatase had fallen from 385 to 126 IU/l. Thereafter treatment with  $1\alpha\text{-HCC}$   $1.35\ \mu\text{g}$  daily was substituted (Fig. 7) and plasma alkaline phosphatase fell to normal. She had bilateral tibial osteotomies (arrow, Fig. 7) for valgus deformities of the knees, and bone taken during the operation showed normal histology contrasting with gross changes of osteomalacia found before treatment with  $1\alpha,25\text{-DHCC}$ . When treatment was stopped (due to lack of supplies) plasma calcium fell, alkaline phosphatase progressively increased, bone pain and abnormal radiological findings recurred. Further treatment reversed these trends and levels of plasma hydroxyproline and iPTH also fell. Treatment was continued intermittently (Fig. 7) and, though levels of alkaline phosphatase remained normal, each break in treatment was associated with a rise in plasma iPTH. In the 2 years since the surgical

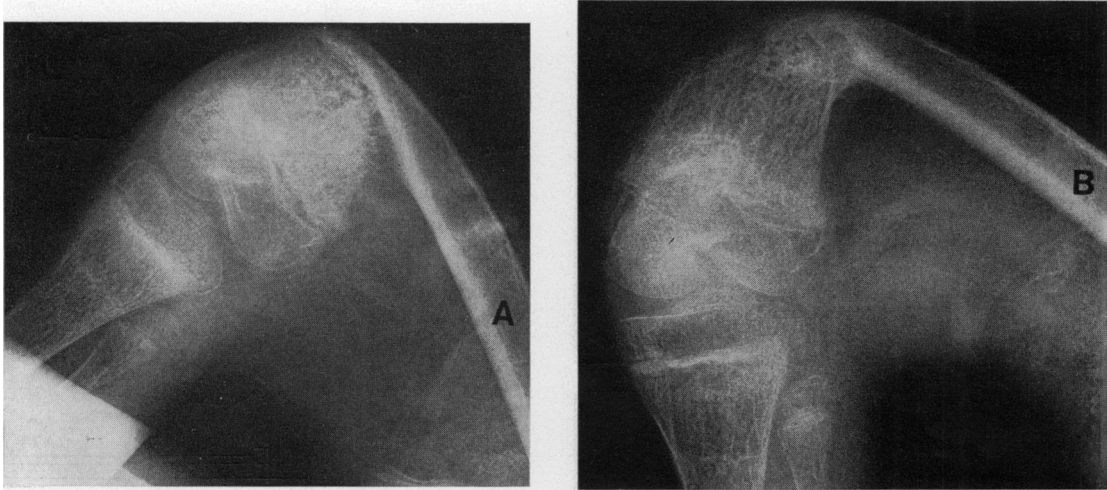


Fig. 6 Case 2. Radiological improvements seen in renal osteodystrophy with improvements of bone resorption. (A) Before treatment; (B) after 20 months' treatment with  $1\alpha$ -HCC 1–2  $\mu$ g daily.

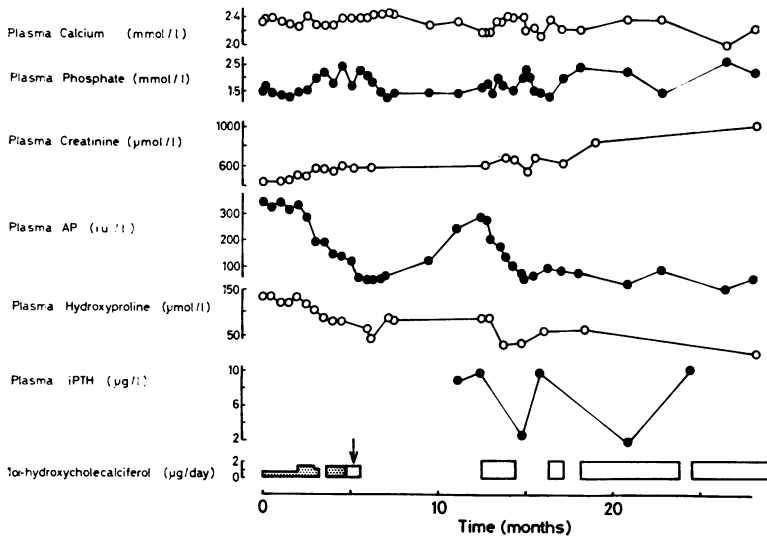


Fig. 7 Case 3. Biochemical responses to  $1\alpha$ -HCC. Before treatment with  $1\alpha$ -HCC she had received  $1\alpha$ , 25-DHCC for 5 months, shown by stippled area at lower left. The arrow indicates the time when bilateral tibial osteotomies for knock-knees were performed.

correction of her deformities there has been no recurrence of knock-knee or pain.

**Case 4.** This patient did not have a bone biopsy before treatment but there was clear x-ray evidence of widespread rickets (Fig. 8). Plasma levels of iPTH were not markedly raised. The immediate response to  $1\alpha$ -HCC while on a constant diet (Fig. 9) resembled that seen in Fig. 1 with a rise in plasma calcium and, after a few days, a fall in the urinary excretion rate of calcium. Plasma

creatinine (not shown) did not change. There was no consistent change in plasma concentration or urinary excretion rate of phosphate and the estimated fasting TmP/GFR was unaltered. With prolonged treatment (Fig. 10) plasma calcium increased further and plasma alkaline phosphatase fell progressively. On 3 occasions when treatment was stopped, plasma alkaline phosphatase increased. Radiographic improvement was striking (Fig. 8); and after 16 months of treatment bilateral femoral osteotomies (arrow, Fig. 10) were performed

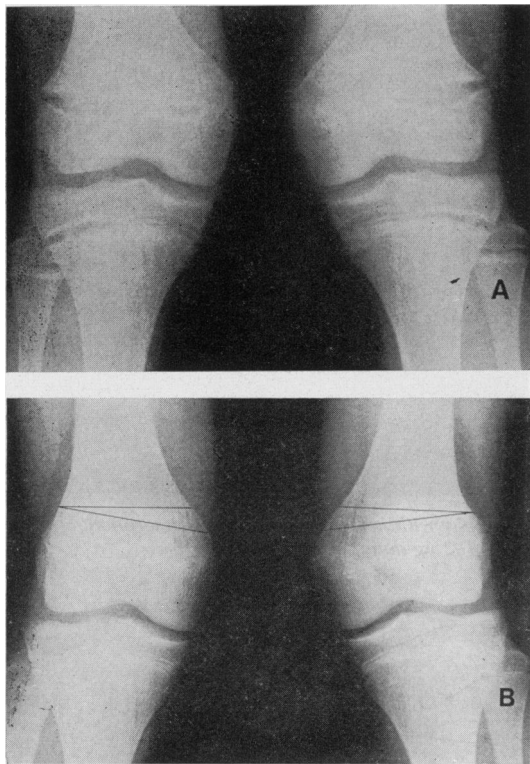


Fig. 8 Case 4. Shows healing of rickets in response to 1 $\alpha$ -HCC to 2  $\mu$ g daily (A) before treatment, (B) after 18 months' treatment. This is a preoperative x-ray, and the lines drawn on the femur indicate the amount of bone to be removed at osteotomy.

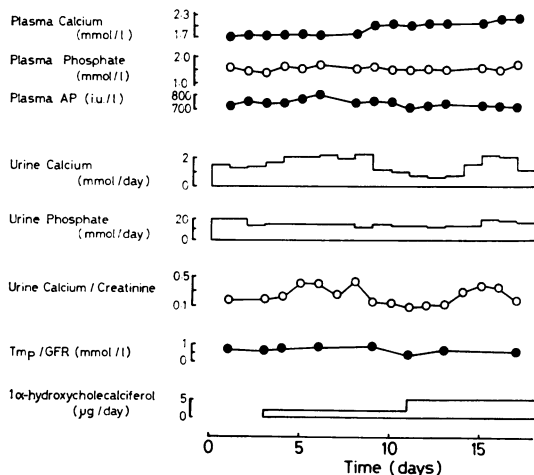


Fig. 9 Case 4 The biochemical effect of 1 $\alpha$ -HCC.

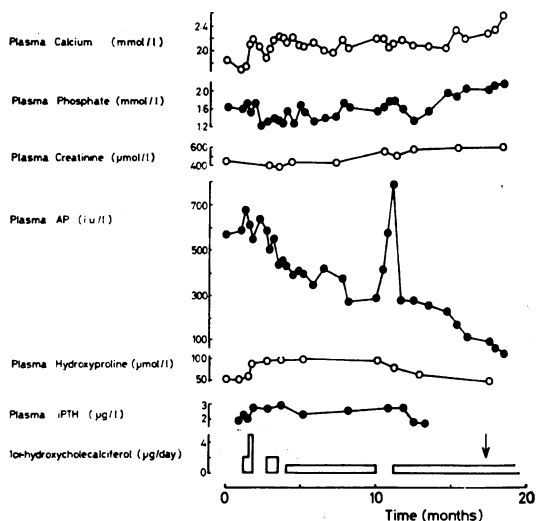


Fig. 10 Case 4. The effect of prolonged treatment with 1 $\alpha$ -HCC. Bilateral femoral osteotomies were performed at the time shown by the arrow.

without complication. Wedges of femoral bone, excised at operation, were histologically normal.

However, despite these improvements, no fall in iPTH or plasma hydroxyproline occurred, indeed they increased during the first 5 months of treatment. As in Case 2, plasma levels of hydroxyproline correlated with levels of iPTH ( $r = +0.78$ ;  $P < 0.02$ , Fig. 5).

### Discussion

Because 1 $\alpha$ -HCC is more easily synthesized than 1 $\alpha$ ,25-DHCC and is probably converted in the body to 1 $\alpha$ ,25-DHCC (Zerwekh *et al.*, 1974), it will probably be more widely available than 1 $\alpha$ ,25-DHCC for clinical use. Investigation of the effects of prolonged administration is therefore important. Previous studies in renal osteodystrophy have shown that relatively large doses of this vitamin D analogue increase intestinal absorption of calcium (Chalmers *et al.*, 1973; Peacock *et al.*, 1974). When given for up to 3 months, reversal of progressive demineralization as judged by regional neutron activation analysis (Catto *et al.*, 1975), improvement of abnormal bone histology, and suppression of raised plasma levels of iPTH (Fournier *et al.*, 1976) may occur. More prolonged treatment in similar patients (Nielsen *et al.*, 1975; Davie *et al.*, 1976; Henderson *et al.*, 1976) have also shown radiographic and biochemical improvements. Recent reports have suggested, however, that not all patients with renal bone disease improve

after treatment with  $1\alpha$ -HCC (Pierides *et al.*, 1976) and that favourable biochemical changes in some patients may be associated with demineralization (Tougaard *et al.*, 1976) and deterioration of bone disease (Naik *et al.*, 1976).

The present 2-year study shows that it is possible to heal renal osteodystrophy with  $1\alpha$ -HCC; it also shows that the response of our patients to  $1\alpha$ -HCC is by no means uniform. All of them were nondialysed, growing adolescents with radiological and histological evidence of severe bone disease in whom bone deformity was progressive, but they differed from each other in the degree of renal failure, the rate of its progression, and the nature and degree of their osteodystrophy.

The biochemical responses to  $1\alpha$ -HCC were largely predictable, but have some points of interest. Plasma calcium increased with treatment and in the 2 patients with predominant osteitis fibrosa it was necessary to stop  $1\alpha$ -HCC lest hypercalcaemia ( $>2.65$  mmol/l;  $>10.6$  mg/100 ml) prejudice their remaining renal function. It is possible that these 2 patients were more sensitive to the metabolic effects of  $1\alpha$ -HCC than those with predominant rickets. Falls in urinary calcium, not associated with falls in plasma calcium or detectable deterioration of renal function and independent of dietary intake, were observed in the 3 patients studied. These observations suggest that  $1\alpha$ -HCC may increase renal tubular reabsorption of calcium, either directly or via PTH.

Plasma phosphate, TmP/GFR, and phosphate balance seemed to alter little at the start of treatment but after the first few days plasma phosphate fell in all patients (except in Case 3, already treated with  $1\alpha,25$ -DHCC). This fall could be due to incorporation of phosphate into bone, a suggestion supported by the positive phosphate balance of Case 2 after 18 months of treatment.

The increased alkaline phosphatase fell in all patients with prolonged treatment, a fall preceded by a temporary 'flare' of activity in Case 1 (Fig. 2). In adolescents, particularly those with chronic renal failure, in whom puberty and growth may be delayed, a decrease in activity of alkaline phosphatase may be difficult to interpret. Nevertheless, in our patients alkaline phosphatase invariably increased when treatment was stopped (Figs. 4, 7, 10) and fell again when it was started, which strongly suggests that it was the  $1\alpha$ -HCC and not increasing maturity which was responsible for these changes.

Although the changes in plasma iPTH were variable, and their interpretation may be complicated by considerations of immunoreactive heterogeneity and uncertain biological activity (Berson and

Yalow, 1971; Reiss and Canterbury, 1973), plasma levels correlated well with other indices of response to  $1\alpha$ -HCC. Thus in Case 1 (Fig. 2) iPTH fell with the improvement of early treatment and increased with the later radiological and biochemical deterioration. Since plasma nonprotein-bound hydroxyproline provides a measure of bone turnover (and particularly of resorption), the observed correlation between this and iPTH in those patients in whom there were sufficient estimations (Cases 1 and 4) suggests that iPTH measurements have biological significance. The overall relationship between plasma iPTH and hydroxyproline for the whole group of patients (Fig. 5) is of interest but may be fortuitous. Since the changes in iPTH during treatment were not always associated with detectable changes in total plasma calcium it is possible, as suggested by animal experiments (Chertow *et al.*, 1975), that the  $1\alpha$  derivatives of vitamin D may directly inhibit PTH secretion. However, the evidence is inadequate in this study, since ionized calcium was not measured.

If the assay for PTH is measuring fragments of biological significance, it appears that suppression of PTH may not be a prerequisite for bone healing in that a favourable biochemical radiological response was observed in one patient without suppression of plasma iPTH (Fig. 10).

Perhaps the most important question which this study answers is whether treatment with  $1\alpha$ -HCC can sufficiently heal renal osteodystrophy to allow sustained surgical correction of deformity (it should be recalled that the main complaint of the 2 girls was progressive knock-knee). In Cases 3 and 4 these aims were achieved. In Case 2 there was convincing radiological evidence of mineralization and healing of excessive resorption (Fig. 6). We did not consider it necessary to confirm this histologically, especially since the deformities were so severe that orthopaedic correction, though feasible, was not justified. In one patient (Case 1) renal osteodystrophy relapsed after an initially good response to treatment, the most obvious reason being his rapidly progressive renal failure. The relapse may also have been due to treatment with propranolol which was started in the sixth month of treatment with  $1\alpha$ -HCC, since there is some evidence in dialysis patients (Heynen *et al.*, 1977) that  $\beta$ -adrenergic blocking drugs may inhibit the secretion of calcitonin. It is unlikely that he had stopped taking  $1\alpha$ -HCC since the initial increase in plasma calcium was sustained. The interesting responses of this patient shows that good results in short-term treatment with  $1\alpha$ -HCC and possibly  $1\alpha,25$ -DHCC do not necessarily mean that long-term results will be equally favourable.

Large doses of vitamin D or dihydroxycholesterol also heal rickets, osteomalacia, or osteitis fibrosa in a proportion of patients with renal osteodystrophy (Dent *et al.*, 1961; Stanbury and Lumb, 1962; Stanbury, 1966; Pendas, 1969). Apart from the question of dosage there is no convincing evidence that  $1\alpha$ -HCC produces therapeutic effects in any way different from those achieved with large doses of vitamin D or 25-hydroxycholecalciferol. The clear advantage of  $1\alpha$ -HCC lies in its predictable effective dose range, which is narrower than that of the parent vitamin, and its shorter duration of action. Thus when we have stopped treatment with  $1\alpha$ -HCC after inadvertently induced hypercalcaemia, plasma calcium returned to normal with a half-time of 2 to 6 days.

We conclude that renal bone disease may be effectively treated with long-term  $1\alpha$ -HCC, but careful supervision of the patient is required. Hypercalcaemia is readily controlled but despite prolonged treatment relapse may occur in some cases.

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*The following articles will appear in future issues of this journal:*

Intramuscular salbutamol in treatment of acute exacerbations of childhood asthma. *P. Thompson and M. Friedman.*

Autoantibodies to Tamm-Horsfall protein in detection of vesicoureteric reflux and renal scarring. *A. Fasth, L. Å. Hanson, and A. W. Asscher.*

Bucolome in prevention of hyperbilirubinaemia in preterm infants. *G. Segni, G. Polidori, and C. Romagnoli.*

Deafness after bacterial meningitis. *H. Jeffery, J. Scott, D. Chandler, and A. E. Dugdale.*

Porcine pancreatin as a source of salmonella infection in children with cystic fibrosis. *A. Lipson and H. Meikle.*

Gastroschisis treated with lyophilized dura. *I. S. Reid and G. Cummins.*

Cause of death in tetanus neonatorum: study of 233 cases with 54 necropsies. *R. Salimpour.*