CURRENT STATUS OF THE MANAGEMENT OF RENAL OSTEODYSTROPHY

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A multitude of reports have indicated that musculoskeletal disorders can influence the quality of life and contribute to the morbidity of end stage renal failure patients [1,2,3,4] The incidence as well as the nature and severity of these complications varies from one centre to another [4,5]. We shall not discuss bone disease following renal transplantation and refer the reader to the recent review by Gottlieb et al [6].

The treatment of renal osteodystrophy aims to interfere with the main pathophysiological mechanisms resulting from the reduction of the renal functional mass and leading to phosphate and divalent cation disturbances, skeletal demineralisation and soft tissue calcification. Detailed discussions appear in recent comprehensive reviews on the subject, either in the English [2,4,7,8] or the French literature [1,3].

Current Concepts of The Pathogenesis of Renal Osteodystrophy

As summarised in the Figure 1, renal osteodystrophy results mainly from the association of osteitis fibrosa (OF) and osteomalacia (OM). OF is characterised by increased osteoclastic and osteocytic osteolysis and increased medullary fibrosis induced by an increase in parathyroid hormone (PTH) secretion. Osteomalacia results from defective mineralisation of bone. When this latter is assessed on bone biopsy not only on the basis of increased osteoid volume or increased osteoid thickness, but also on the basis of decreased mineralisation front and decreased mineralisation rate, evaluated with double tetracycline labelling, it is much less frequent than osteitis fibrosa [1]. Osteosclerosis, mainly seen in vertebrae, may also be the result of hyperparathyroidism and is due to an excess of woven bone, i.e. bone without lamellar disposition mineralising quite easily without vitamin D but having inferior mechanical qualities [9].
Mechanisms of Secondary Hyperparathyroidism

PTH secretion is stimulated during renal insufficiency by two major mechanisms which tend to lower plasma ionised calcium: hyperphosphataemia and acquired vitamin D resistance.

The role of hyperphosphataemia in stimulating PTH secretion is now well established, either in dogs [10] or in man [1]. However, the recent work of Rutherford [10] shows that the proportional reduction of phosphorus intake with the reduction of GFR prevents secondary hyperparathyroidism of uraemic dogs just for one year and that addition of 25 OH vitamin D₃ (20 μg 3 times a week) is necessary to prevent the increase of PTH levels after this time. Furthermore, the trade-off theory of Bricker and Slatopolsky alone cannot account for the initiation of hyperparathyroidism in early renal insufficiency. As a matter of fact, in this situation some patients may have hypocalcaemia and hypophosphataemia [3], whereas according to the trade-off theory plasma phosphate should either be transiently elevated or normal.

Acquired resistance to vitamin D Since the early work of Dent and Stanbury [7], it is well known that uraemia induces a state of resistance to vitamin D, i.e. a state characterised by abnormalities commonly seen in vitamin D deficiency. These include decreased intestinal absorption of calcium, hypocalcaemia, delayed mineralisation of osteoid and secondary hyperparathyroidism, which are corrected only with pharmacological doses of vitamin D or its analogue, dihydrotrachysterol (DHT).

The kidney is the only organ able to hydroxylate 25 OH vitamin D₃ in position 1 to form 1α,25 (OH)₂D₃ [11,12]. This metabolite is considered to be the hormonal form of the vitamin because it is the most potent metabolite in increasing intestinal absorption of calcium and in mobilising calcium from the bone. 1α-hydroxylase activity and plasma concentrations of 1α,25 (OH)₂D₃ have been shown to be decreased or absent in uraemic or anephric patients. Liver 25-hydroxylase activity is normal in these patients, which explains why plasma concentrations of 25 OH D are normal, provided these patients are not put on a low protein diet with dairy restrictions, which decreases the vitamin D intake or on anticonvulsant therapy which increases 25 OH D catabolism to inactive metabolites. The decrease in 1α-hydroxylase activity is related mainly to the reduction in functional nephron mass, to hyperphosphataemia and probably also to acidosis [13].

Although the dose of 1α,25 (OH)₂D₃ necessary to increase active calcium absorption in non-uraemic man is 0.14 μg/day, whereas it is 0.68 μg/day in the uraemics, it is reasonable to consider that lack of 1α,25 (OH)₂D₃ is the main mechanism of this calcium malabsorption [14]. This latter leads to a negative calcium balance when the dietary intake of Ca is below 2 g of elemental Ca. This is usually the case in renal insufficiency, the average calcium intake being 1 g in a normal adult, and around 400 mg in uraemic patients because of their low protein diet and restriction in dairy products.
Decreased active calcium absorption and low plasma levels of 1α,25 (OH)₂D₃ have been reported however only in advanced renal insufficiency, i.e. when the GFR falls below 30 ml/min. In mild renal insufficiency, normal levels of 1α,25 (OH)₂D₃ have been found together with high levels of PTH, suggesting a relative deficiency in 1α-hydroxylase activity since high levels of PTH should normally be associated with increased 1α-hydroxylase activity [3]. Furthermore, low plasma concentrations of Ca and PO₄ and a decreased hypercalcaemic response to exogenous or endogenous PTH in spite of histological evidence of osteitis fibrosa were also observed in such situations. To explain these paradoxical findings, Llach et al [15] proposed that transitory post-prandial increase in plasma PO₄ may lead to an increase in intracellular PO₄ and hence to a decrease in 1α,25 (OH)₂D₃ production. Relative 1α,25 (OH)₂D₃ deficiency would be the cause of early skeletal resistance to the calcemic action of PTH and therefore of PTH secretion stimulation. As a matter of fact, although hyperparathyroidism per se could contribute to this decreased calcemic response to exogenous PTH, as demonstrated by Pavlovitch et al in the rat [16], the fact that this decreased response is still observed after parathyroidectomy in man and dog [8,17], shows that bone resistance to PTH can be considered as a causal mechanism rather than a consequence of increased PTH secretion. Preliminary results showing that phosphate restriction in early renal insufficiency restored the calcemic response to PTH support this hypothesis [15]. Decreased production of 1α,25 (OH)₂D₃ is however probably not the whole explanation of the vitamin D resistant state. We have observed that the doses of 1α,25 (OH)₂D₃ necessary to normalise intestinal calcium absorption in uraemic man were greater than in normal man. Furthermore, in thyroparathyroidectomised dogs, Massry [17] has shown that 1α,25 (OH)₂D₃ completely corrected the skeletal resistance to PTH in dogs in which uremia was induced by urine diversion into a vein, but that in nephrectomised dogs correction was incomplete. This implies that other factors may be involved, one of which might include decreased production of 24,25 (OH)₂D₃. This metabolite is also formed mainly but not exclusively by the kidney and its plasma concentrations are decreased in uraemia [18]. Although it has up to now been considered only as an excretory by-product of vitamin D, because of its low biological activity in animals, and because its synthesis is inversely proportional to that of 1α,25 (OH)₂D₃, it may have a physiological role [18]. Indeed, it has been found to increase calcium absorption at a daily dose of 1-10 μg even in anephric men [19]- results not confirmed however by Pierides [19]- and to be more potent than 1α,25 (OH)₂D₃ in decreasing PTH secretion of the parathyroid glands of goats or dogs when injected into the arteries of isolated glands [21]. Although cellular receptors for 1α,25 (OH)₂D₃ have been demonstrated in the parathyroid cells, the effect on PTH secretion is not clear because of conflicting experimental results and of the failure in man to demonstrate a direct inhibitory effect [18,21]. Therefore, it is possible, although not proved, that lack of 24,25 (OH)₂D₃ could contribute to stimulation of PTH secretion by increasing this secretion for any given plasma calcium concentration and by contributing to the calcium malabsorption.
Other factors contributing to osteitis fibrosa  Recently Kanis et al have sugges-
ted that calcitonin could protect the bone against PTH hypersecretion [1].

Increased plasma levels of PTH in uraemia are the result not only of an
increased secretion of PTH but also of decreased degradation. The kidneys
are able to take up both intact PTH and its fragments, whereas the liver is
only capable of taking up intact PTH. Therefore, degradation of PTH frag-
ments and especially of the C terminal fragments is impaired in chronic renal
failure, contributing to increased plasma levels. Since, these fragments are
thought to be biologically inactive, the clinical significance of the increase is
dubious [22].

Pathophysiological Mechanisms of Renal Osteomalacia

Mainly on the basis of animal studies, it is generally assumed that vitamin D
corrects the mineralisation defect of vitamin D deficiency indirectly, by in-
creasing the calcium and phosphate concentration in the bone extracellular
fluid through stimulation of intestinal absorption and renal tubular reabsorp-
tion of these ions and stimulation of their release from previously calcified
bone. Since 1α,25 (OH)\(_2\)D\(_3\) is the most potent metabolite in increasing in-
testinal calcium transport and in stimulating bone resorption, lack of 1α,25
(OH)\(_2\)D\(_3\) in uraemia is the logical explanation for renal osteomalacia [11,12].
A number of clinical observations suggest however that 1α,25 (OH)\(_2\)D\(_3\) can-
not be the sole metabolite responsible for bone mineralisation. Bordier et al
pointed out that anephric patients may have normal osteoid volume and a
normal mineralisation front [1]. Jubiz et al showed that in patients on anti-
convulsant therapy who are prone to osteomalacia, plasma concentrations of
1α,25 (OH)\(_2\)D\(_3\) are normal or increased whereas those of 25 OH D are de-
creased [12]. In the vitamin D deficient adult, 1α,25 (OH)\(_2\)D\(_3\) only partially
corrects the decreased mineralisation front which is normalised either by
25 OH D\(_3\) alone or by the combination of 1α,25 (OH)\(_2\)D\(_3\) and 24,25 (OH)\(_2\)
D\(_3\) [23]. 1α,25 (OH)\(_2\)D\(_3\) does not consistently correct the osteomalacic
component of uraemic patients [24] and in uraemic patients, 1α OH D\(_3\) in-
duces a smaller increase in the mineralisation front than 25 OH D\(_3\) in spite
of a greater increase in the plasma calcium phosphate product [25].

Before accepting these last three observations as argument against the unique
role of 1α,25 (OH)\(_2\) vitamin D\(_3\) in mineralising bone, measurements of 1α,25
(OH)\(_2\)D in the plasma and the target organs are necessary to evaluate the ex-
tent to which intermittent administration of 1α-hydroxylated derivatives may
reproduce physiological plasma and tissue concentrations. Other clinical ob-
servations suggest that vitamin D acts directly on the mineralisation process :
- in uraemic patients, increasing the calcium phosphate product by increasing
the oral intake of calcium and phosphate induces abnormal and patchy min-
eralisation of the osteoid but does not normalise the mineralisation front
whereas this does occur with vit D\(_2\) or 25 OH D\(_3\) (Eastwood cited in 1). In
uraemic patients, the increase in mineralisation front is negatively correlated
with the increase in the plasma calcium phosphate product when vitamin D
metabolites are given when the other therapeutic measures, and especially the
doses of phosphate binders, are kept constant [25].

Since lack of 1α,25 (OH)₂D₃ cannot be the whole explanation for renal osteomalacia, which vitamin D metabolite would be specifically involved in the mineralisation process? Eastwood has proposed 25 OH D₃ itself on the basis that in non-dialysed uraemic patients, osteomalacia was seen only in patients with low plasma levels of 25 OH D [26]. The cause of these decreased levels are multiple; although the absorption of vitamin D in uraemia is normal, the intake is usually reduced because of the low protein diet and the restriction in dairy products advised to prevent hyperphosphataemia. Furthermore, uraemic patients may have increased hepatic microsomal enzyme induction leading to increased 25 OH D₃ catabolism, even when they do not take anticonvulsant therapy. Although the decrease in plasma concentration of 25 OH D₃ can contribute to osteomalacia, this cannot be the main mechanism of renal osteomalacia, as the mineralisation defect can be encountered in the presence of normal or elevated plasma concentrations of 25 OH D₃ [9,25] and that in these cases, only pharmacological doses of 25 OH D₃ can correct it. Therefore, it is logical to suggest that another metabolite of 25 OH D₃, the formation of which is decreased in uraemia, could be involved. 24, 25 (OH)₂D₃ might be the candidate for the following reasons: its levels are decreased in uraemia [18], it increases incorporation of ³⁵SO₄ into chondrocytes in vitro [18], it normalises the mineralisation front of vitamin D deficient men in combination with 1α,25 (OH)₂D₃ [23].

Occasionally, osteomalacia encountered in chronic renal failure may be due to phosphate depletion. This is usually caused by overcorrection of hyperphosphataemia with phosphate binders [1,2] but has also been observed in the absence of these binders [1]. These rather rare cases have been observed mainly in England and attributed to low PO₄ intake and/or to phosphate malabsorption, in which lack of 1α,25 (OH)₂D₃ might be involved.

Other factors may interfere with bone mineralisation: acidosis, hypermagnesaemia, increased levels of pyrophosphatase and the uraemic calcification inhibiting factor of Yendt, which is probably a polypeptide, since it is removed by peritoneal dialysis but not by dialysis with cuprophane membrane. The reader is referred to general reviews for critical evaluation of these factors [1,2,3,4,7,8]. Furthermore, uraemia induces a defect in bone collagen synthesis which may play a role in the subsequent mineralisation process [4]. In rats, this defect is corrected by 25 OH D₃. Whether 1α-hydroxylated compounds are also effective is not known.

Pathophysiology of the Soft Tissue Calcification

The non visceral calcifications (periarticular and vascular) are made up of hydroxyapatite and are mainly related to the increased calcium phosphate product and the associated elevated PTH levels. Their incidence is very high when the product is greater than 70 and decreases when the product is lowered by phosphate binders and/or parathyroidectomy [1,2]. In some rare cases of overt secondary hyperparathyroidism, the vascular calcifications are associated with skin ulceration and tissue necrosis.
The visceral calcifications (lung, heart, muscles, kidneys) are made up of amorphous microcrystals of Ca, Mg and PO₄. They are dependent upon increased magnesium concentrations rather than upon the calcium phosphate product [1,2,8].

Calcium deposition may be increased in the skin but the causal relationship of this to pruritus is not certain.

**Neuromuscular Abnormalities**

Renal osteodystrophy may be associated with neuromuscular abnormalities in which secondary hyperparathyroidism and active vitamin D metabolite deficiency have been incriminated. Distal muscle weakness especially if associated with sensory abnormalities, is most likely due to uraemic neuropathy. Since a correlation between PTH levels and nerve conduction velocity has been found, hyperparathyroidism may be partially responsible for this neuropathy [27].

Proximal painless muscle weakness seems to depend mainly on the deficiency of active vitamin D metabolites or occasionally on hypophosphataemia. Though a specific cellular receptor has been found in the muscle only for 25 OH D₃ and not for 1α,25 (OH)₂D₃, it is not certain that 25 OH D₃ is the specific muscular metabolite of vitamin D. This proximal muscle weakness in uraemic patients has been improved by 1 μg of 1α,25 (OH)₂D₃ [1,2,4] as well as by pharmacological doses of 25 OH D₃.

Painful proximal muscle weakness has been related to muscle ischaemia due to arterial calcifications of overt hyperparathyroidism [2]. Another complication of severe hyperparathyroidism, which is often ignored, is the rupture of muscular tendons, especially the patellar tendon [1,2,8].

**Management of Renal Osteodystrophy In Mild Renal Insufficiency (GFR > 30 ml/mn)**

Though it would be intellectually gratifying to prevent the development of renal osteodystrophy as soon as the pathophysiological mechanisms and historical lesions are known to occur, i.e. as soon as GFR is less than 80 ml/min we are not willing to impose early restrictions on these asymptomatic patients since the clinical benefit has not yet been proved. Furthermore, because of the potential hazard of long term administration of aluminium-containing phosphate binders, we do not recommend their prescription in early chronic renal failure with normal or low plasma levels of phosphate.

The only measure that we would recommend is an oral supplement of a basic calcium salt as calcium carbonate at a daily dose of 3 g, i.e. 1.2 g of elemental calcium to correct acidosis and bring the oral calcium intake to around 2 g, i.e. an amount at which calcium balance is achieved even without 1α,25 (OH)₂D₃ being available. This measure seems to us sufficient in adults on an unrestricted diet, without heavy proteinuria and not taking anticonvulsants.

However, since plasma 25 OH D levels are decreased in the nephrotic syn-
drome because of loss of 25 OH D with the proteinuria, as well as during anticonvulsant therapy because of enhanced catabolism to inactive metabolites, vitamin D or 25 OH D₃ supplements are recommended in these patients controlled by plasma levels of 25 OH D. Such measures are also recommended during corticosteroid therapy because corticoids decrease calcium absorption (probably by an increased catabolism of 1α,25 (OH)₂D₃ in the intestinal wall).

For children, paediatricians recommend systematic supplements of vitamin D as soon as the GFR is below 60 ml/min/1.73 m². either as vitamin D₂ or vitamin D₃ at a daily dose of 100 to 300 µg or as 25 OH D₃ at a dose of 25-50 µg. Use of multivitamin preparations should be avoided since they usually contain vitamin A which accumulates with renal insufficiency and stimulates PTH secretion.

At this stage of renal insufficiency, annually and then half-yearly and quarterly estimations of plasma concentrations of calcium, phosphate and alkaline phosphatase are useful, to be certain that they remain in the normal range in spite of the progressive fall in the creatinine clearance.

Management of Renal Osteodystrophy In Advanced Renal Insufficiency (GFR 5 ml to 30 ml/min)

Management of Overt Renal Osteodystrophy

Biochemical and radiographic abnormalities At this stage, plasma calcium begins to decrease and plasma phosphate to increase. In some cases, especially those with a very slow decrease in GFR and a greater degree of acidosis (like polycystic kidneys and renal failure secondary to a uropathy), serum bone alkaline phosphatase increases and radiological abnormalities of osteodystrophy develop. They will be detected on the annual bone survey which includes X-rays of the hands, skull, chest, spine, pelvis, elbows, knees and feet.

Subperiosteal erosion of the phalanges is by far the most sensitive and specific radiographic sign of hyperparathyroidism. It usually begins on the radial side of the middle phalanx of the 2nd finger. Less specific is the acroosteolysis of the tuft of the terminal phalanx [29]. Later subperiosteal resorption may be observed on the metaphyses (upper end of the tibia, neck of the femur and humerus, lower end of the radius and ulna) and beneath the sites of tendon attachment. Subchondral resorption occurs especially at both ends of the clavicle, at the sacroiliac joint and the pelvic symphysis. Granular mottling of the skull is another early sign of hyperparathyroidism. In more severe cases, intracortical resorption occurs giving longitudinal striae in the cortex of the phalanges and a wormy-wood appearance in the long bones. Whereas, the periosteal neostosis of Meena is a rather rare finding, osteosclerosis is a common finding in advanced renal osteodystrophy. It is mainly confined to the end plates of the vertebrae giving the ‘rugger jersey spine’.

Specific radiographic abnormalities of osteomalacia, like the Looser zones or biconcavity of the vertebrae are more rarely observed. Decreased mineralocytency, because of the coarsening of the trabeculae, is more frequent but related both to osteomalacia and osteitis fibrosa [29].
Osteoporosis in the strict sense of a reduction in bone mass is rarely observed in renal osteodystrophy, since bone volume is usually normal or increased. However, localised osteoporosis may be seen. Thus, a loss of cortical bone as measured on the phalanx is a usual finding. Bone rarefaction of the metaphyses is however quite rare before maintenance dialysis.

Fractures may be seen eventually. They are mainly stress fractures localised to the metatarsals and the ribs.

Before skeletal maturity, other radiographic findings may be observed [29]. In infancy and childhood all the classical signs of 'rickets' may occur including enlargement of the epiphyseal growth plate and the metaphysis at the costochondral junction, wrists and other joints. These findings are due to true delay of mineralisation of the uncalcified cartilage of the epiphyseal plate, but this appears to be much less common than 20 years ago. As the Heidelberg group has shown, Albright and Reifenstein's statement: "renal rickets is not rickets at all but osteitis fibrosa generalisata", is much closer to the truth today than at the time it was made [29]. The radiological ricket-like lesions of hyperparathyroidism are characterised by a normal epiphyseal lucent zone and by severe irregularities of the metaphyseal zones, extending to subperiosteal resorption of the cortex of the metaphysis.

In adolescence, the main bone complications of renal failure are genu valgum due to a collapse of the outer side of the lower femoral metaphysis and slipping of the epiphysis, the most common site being the femoral capital epiphysis.

In addition to these bone abnormalities, the X-ray survey may show soft tissue calcification and in more severe cases clinical symptoms may occur, including pseudogout, muscle weakness, tearing of muscular tendons and bone pain.

_Treatment_ When such radiological or clinical findings are present, or even when only a decrease in bone mineral content is found by photon absorption technique, it is logical to use all the therapeutic measures available to counteract the pathophysiological mechanisms, i.e. the hyperphosphataemia, acidosis, and vitamin D resistance.

Control of hyperphosphataemia and acidosis is based on both dietary restrictions and the use of phosphate binders. Dietary restriction of phosphate to 700–900 mg can be obtained by protein restriction from 60 to 40 g/day with avoidance of dairy products. Because of protein malnutrition and unpalatability, more severe protein restriction is to be avoided. Since these dietary measures are insufficient to keep plasma phosphate in the normal range, administration of calcium and aluminium compounds to bind intestinal phosphate is necessary.

Oral supplement of calcium, either as a carbonate (40% Ca), lactate (13% Ca) or gluconate (9% Ca) can decrease phosphate absorption [1]. Furthermore, at high dosage (more than 2 g per day) calcium may be absorbed passively without 1α,25 (OH)₂D₃ and this corrects the negative calcium balance and the acidosis. Therefore, we recommend the systematic administration of such supplements. Since, in this situation of overt renal osteodystrophy, we rec-
ommend vitamin D supplements, a supplement to bring total oral calcium intake to 1.5 g is sufficient. In practice, we prescribe 3 g, or a heaped teaspoon of calcium carbonate powder which is cheap and relatively well tolerated, in preference to proprietary preparations as Titralac (Riker Laboratories), which provides 160 mg of elemental Ca or of Calcium SANDOZ which provides 500 mg of elemental Ca per tablet. These preparations are more expensive. Furthermore, Calcium SANDOZ contains 13 mEq of sodium bicarbonate per tablet, which may cause sodium overload and alkalosis with tetany in spite of a normal total calcium. Calcium chloride should be avoided in azotaemic patients, because it produces metabolic acidosis.

Aluminium compounds to bind phosphate in the intestine are almost always necessary because hyperphosphataemia is not well controlled solely by dietary restriction and an oral calcium supplement. These compounds include: aluminium hydroxide either in tablets (as Aludrox®, Polysilane®), in powder (as Thymobiol®) or in gel (as Lithiagel®); aluminium tyrosinate in tablets (Al₃O₇®) and aluminium carbonate (Basageï®). The use of mixed preparations containing magnesium is not recommended because it induces hypermagneisaemia. Preparations of calcium and aluminium, such as Ulfon® are to be avoided, because of the danger of hypercalcaemia.

Aluminium containing phosphate binders do not represent an ideal therapeutic tool, since they are often poorly tolerated, sometimes induce severe constipation and even intestinal obstruction or perforation. Their incorporation into cookies or bread sticks may make phosphate binders more tolerable. Aluminium in all these preparations is partially absorbed [1,30] and this represents a potential long term hazard, since aluminium in the dialysate has been incriminated in the pathogenesis of dialysis dementia and dialysis osteomalacia [5,31]. Although the toxicity of the aluminium in phosphate binders has not been proved [33], this potential hazard should stimulate the search for a non toxic phosphate binder. The use of an anion exchange resin may prove to be a better approach.

Aluminium compounds have to be used with caution and any central nervous system symptoms, such as dysarthria or dyspraxia must prompt the determination of serum aluminium. If this latter is above 200 µg/L, phosphate binders must be stopped and dialysis of greater frequency and duration with stricter diet or parathyroidectomy must be considered.

The optimal range for plasma phosphate in uraemic patients not yet on dialysis is still controversial. Bishop et al [1] suggest that the normal range, i.e. 3.0 - 4.2 mg/dl (0.85 - 1.2 mmol/L) in the adult and 3.5 - 5.5 mg/dl (1.0 - 1.5 mmol/L) in the child might be below the optimal one since they observed increased osteoid volume in their patients when plasma phosphate was below 2 mmol/L, i.e. 7.0 mg/L. Considering that overt osteomalacia has only been observed in hypophosphataemic patients and that a plasma phosphate of 2 mmol/L definitely leads to worsening of hyperparathyroidism, we recommend the normal range as the optimal one, hoping that the simultaneous use of vitamin D will prevent the increase of osteoid volume which was observed in patients not taking vitamin D.
Effectiveness and dosage of the various vitamin D sterols Parent vitamin D₂ or D₃ have been used at a daily dose of 0.5 - 12 mg per day, but the starting dose recommended was only about 1 mg or even lower when the PCa was above 9.0 mg/L. The high dosage necessary is explained by the fact that the feedback inhibition of 25 hydroxylase has to be overcome in order to induce high plasma levels of 25 OH D. The parent vitamins have been shown to be effective in curing both osteomalacia and overt hyperparathyroidism with vascular calcifications [1]. However, because of the wide variability in its effective dosage, in part due to the chemical instability of certain preparations, its cumulative storage and the protracted periods of hypercalcæmia (sometimes months), parent D vitamins are now less frequently used except as a small supplement in cases of low intake or low sunshine exposure, when low plasma 25 OH D concentrations may be found. In such cases, a supplement of 400 IU or 10 µg is adequate to maintain normal plasma levels of 25 OH D.

Dihydrotachysterol (DHT) is a synthetic compound which does not require prior renal 1α hydroxylation for biological activity, since the hydroxyl in position 3 is placed stereochemically in position 1 (because of the transposition of ring A around the double bond 5 - 6). Furthermore, its 25 hydroxylation in the liver is not feedback inhibited, so that DHT is more potent than parent vitamin D in renal failure. Kaye et al [1] have shown that a daily dose of 250 - 370 µg increases calcium absorption and reduces osteitis fibrosa and Hill has shown that osteomalacia may be cured in about 50% of cases after 7 - 20 months of administration [2]. Hypercalcæmia when it occurs, disappears usually within 10 days following discontinuation of DHT [2,33].

25 OH vitamin D₃ is now available for hospital use in several European countries. The doses required to produce a beneficial effect in uraemic patients vary between 40 and 125 µg per day. Its advantage over parent vitamin D is obvious, since it bypasses hepatic hydroxylation and is less likely to be stored in body fat or muscles. This explains why hypercalcæmia decreases within a week and completely disappears within 4 weeks after its discontinuation, making this drug less hazardous than the parent vitamin D [25]. Its advantages over DHT are more theoretical than practical. No controlled comparative study has yet been done. Since 25 OH D₃ is a natural metabolite and 1α,25 (OH)₂ D₃ may not be the sole active metabolite, 25 OH D₃ may have a more complete action than DHT, especially in treating osteomalacia. Furthermore, measurement of plasma 25 OH D can provide therapeutic information whereas levels of DHT cannot be measured. Finally, since DHT requires 25 hydroxylation to become active, it may be less active when the patient is taking anticonvulsants.

The effectiveness of 1α OH vitamin D₃, the synthetic analogue of 1α,25 (OH)₂ vitamin D₃, in renal failure is explained by the hydroxyl in position 1 making the renal 1-hydroxylation unnecessary. It must however be hydroxylated in the 25 position by the liver in order to become active. This explains why 1α OH D₃ has been found less active when used concomitantly with anticonvulsants (Pierides cited in 1). Therapeutic trials have shown that it is
effective in increasing intestinal calcium and phosphate absorption, in decreasing plasma alkaline phosphatase and PTH and in reversing histological and radiological indices of osteomalacia or osteitis fibrosa at a daily dose of 0.5 - 2 μg [34]. Since the plasma half-life of 1α,25 (OH)₂D₃ levels induced by administration of 1α OH D₃ is less than 24 hours [36], daily dosage is recommended [35]. The main advantage of 1α OH D₃ over previous compounds is its shorter biological activity, so that after 2 months of administration, hypercalcaemia disappears within a week of stopping treatment [25]. However, in a controlled comparative study, we have shown that it is less effective than 25 OH D₃ in increasing the mineralisation front, despite a greater increase in the plasma calcium phosphate product [25]. This suggests that 1α OH D₃ has a less complete action than 25 OH D₃ in mineralising bone and that therefore it would be less appropriate for the correction of renal osteomalacia than 25 OH D₃. Therefore, we would recommend 25 OH D be given when osteomalacia appears to be the dominant lesion. Our study indicated also that the increase in PCa and the decrease in PTH is the same with both drugs, so that there is little reason to prefer one to the other in treating hyperparathyroidism.

Using 1α,25 (OH)₂ vitamin D₃ intestinal absorption increases in most uraemic patients with a dose of 0.68 μg/day, but hypercalcaemia (most likely due to the permissive effect of vitamin D on PTH induced resorption) has been observed in patients receiving only 0.14 μg/day [2]. This dosage range indicates that a mean daily dose of 0.5 - 1 μg/day should rarely be exceeded. Its effectiveness appears to be greater in healing osteitis fibrosa than renal osteomalacia. However, most of the patients who show no improvement in renal osteomalacia are on chronic haemodialysis with undeionised water and therefore potentially exposed to water toxins [5], or had phosphate depletion [36]. In patients not yet on dialysis, 1α,25 (OH)₂D₃ at a dose of 0.5 μg/day for 4 - 16 months has been shown to cure severe osteomalacia [37]. It is not possible to decide, from the report of Coburn last year, whether the ineffectiveness of 1α,25 (OH)₂D₃ on osteomalacia was exclusive to patients on chronic haemodialysis [24].

Although 1α,25 (OH)₂D₃ is more difficult to synthesise and is not yet available except for clinical research, it may have some advantages over 1α OH D₃ since it bypasses both hepatic and renal hydroxylation and can be used successfully in patients on anticonvulsant therapy; and it is more effective than 1α OH D₃ in promoting calcium absorption at lower doses (0.5 μg/day of 1α,25 (OH)₂D₃ is equivalent to 2 μg of 1α OH D₃).

The advantage of 1α,25 (OH)₂D₃ over 25 OH D₃ resides mainly in its shorter biological action (Brickman, 1976, cited in 1).

Because of the transposition of ring A in 5 - 6 Trans 25 OH vitamin D₃ [38], the hydroxyl in position 3 is placed in position 1 and might therefore not require 1α hydroxylation for activity. However, the effective dose is greater than 50 μg. At this dosage, osteoid volume decreases in most cases, whereas resorption does not change after 9 months. At higher doses (100 - 250 μg/day), resorption is increased and we do not recommend this preparation.
General guidelines for the choice and use of vitamin D in renal osteodystrophy

The possible direct role of vitamin D in collagen synthesis, in the mineralisation process and in the suppression of PTH secretion, leads us to recommend the systematic use of vitamin D supplements in radiologically obvious renal osteodystrophy, regardless of the preponderance of osteitis fibrosa or of osteomalacia, since the pathophysiological mechanisms of both these lesions are related to vitamin D resistance. Vitamin D therapy is especially indicated in children in whom bone deformity may occur rapidly in association with stunted growth.

Although comparative studies of the relative efficiency and safety of the various vitamin D sterols in the treatment of renal osteodystrophy are still needed, we presently prefer to use 25 OH D₃, a natural metabolite present in the plasma. Its plasma half life is 12 days after a single administration [1]. Although pharmacological doses are needed (50–100 µg/day in the adult), it may have greater potential than 1α,25 (OH)₂D₃ or 1α OH D₃ since it may also increase plasma 24,25 (OH)₂D concentration.

Whatever vitamin D-like compound is used, plasma concentration of calcium and phosphate must be carefully monitored and monthly or quarterly determinations of serum alkaline phosphatase must be made. Treatment should not be started before plasma phosphate is decreased to less than 4.5 mg/dl. When the elevated serum alkaline phosphatase is normalised and plasma calcium increases above 9.5 mg/dl, dosage of 25 OH D₃ should be decreased to 50 or even 25 µg/day, that of 1α OH D₃ to 0.5 µg/day and of 1.25 (OH)₂D₃ to 0.25 µg/day. This maintenance dosage should be maintained indefinitely or until successful transplantation. Plasma phosphate generally increases with vitamin D therapy and the dosage of phosphate binders may need to be increased to keep it below 4.5 mg/dl. This control is critical to prevent increases in soft tissue calcification and possibly in osteoclastic resorption [39]. When the above mentioned maintenance doses induce permanent hypercalcaemia (PCa > 10.5 mg/dl) in spite of reduction of oral calcium intake to 1 g, or a permanent hyperphosphataemia (PPO₄ > 6.0 mg/dl), surgical parathyroidectomy should be considered (see below).

Half yearly, a selected bone survey and slit lamp examination of the eye should be performed. When possible, measurement of bone mineral content by photon absorptiometry, calcium measurement by neutron activation of the hand or of the whole body, and bone biopsies with histomorphometry may be performed.

Management of Renal Osteodystrophy not Detectable on X-rays

When radiological and clinical symptoms are absent and the serum alkaline phosphatase is normal, should all the above measures be used in order to prevent the appearance of overt renal osteodystrophy?

Because of the rapidity with which severe deformities may occur in children, paediatricians recommend control of hyperphosphataemia, calcium supplements of 1.5 g/day, and use of vitamin D as 25 OH D₃ at a dose of 25 µg - 50 µg/day.
In adults, before accepting such measures, one must recall the only controlled study performed by Touggaard [1] with 1α OH D₃. A daily dose of 1 μg for 11 weeks normalised calcium absorption and hypocalcaemia and decreased the raised PTH levels, but bone mineral content decreased to the same extent in the treated patients as in the controls. Furthermore, the fall in GFR was 2.5 times greater in the 1α OH D₃ treated group than in the placebo group. Although this difference was not significant, it suggests that 1α OH D₃ treatment may be deleterious to renal function. We cannot therefore recommend its systematic use in the absence of radiological or clinical symptoms. Until results of other studies are available, we would recommend control of the plasma concentrations of calcium and phosphate by oral calcium supplements and by phosphate binders only.

Management Of Renal Osteodystrophy During Maintenance With Artificial Kidneys

Renal Osteodystrophy and Chronic Haemodialysis

The additional pathophysiological factors introduced by chronic haemodialysis are represented in Figure 1 by the stippled and shadowed boxes. They concern mainly the concentration of calcium and magnesium in the dialysate, the purity of the water used for preparation of the dialysate, the schedule and duration of the dialysis. Less important are the use of heparin and the nature and surface of the membranes. The variation of these factors from one centre to the other is the most likely explanation for the wide geographical variations in the incidence of overt renal osteodystrophy.

Dialysate calcium concentration (DCa) Verbeckmoes in 1966 and Wing in 1968 [see 1] showed that DCa should not be below the patients ultrafiltrable calcium to prevent negative calcium balance during dialysis. Subsequently, we showed [49] that bone disease was more frequent when DCa was ≤5.7 mg/dl, because of the greater degree of hyperparathyroidism. In support of this is the contrast between the high incidence of bone disease and the severity of hyperparathyroidism, even after transplantation, encountered in centres like the Peter Bent Brigham which used a DCa of 5.4 mg/L (Plekta cited in 1) and the low incidence of bone disease and the usual decrease of elevated plasma concentrations of PTH in the patients of the Mayo Clinic [41], where a DCa of 7.5 mg/dl was used for a dialysis of 6 hours three times a week together with deionised water and strict control of predialysis phosphate without vitamin D therapy. Control of hyperphosphataemia appeared to be critical for the prevention of calcinosis, for decreasing PiPTH and for favouring net calcium influx during dialysis [42].

Although radiological and biochemical improvement of the patients of the Mayo Clinic was evident, the few bone biopsies performed showed that histological bone resorption was still increased. The beneficial effect of a Dca of 7.5 - 8.0 mg has not been confirmed by everybody. Druke even showed that a DCa of 8.0 mg could stimulate the osteoclasts [42]. Vitamin D resistance
is not corrected by haemodialysis. Since this therapy will correct the negative calcium balance, a high DCa may no longer be necessary and may on a long term basis even be a potential hazard by increasing the extra-skeletal calcium mass of the body. Provided that vitamin D therapy is used, we think that the optimal DCa may be around 6.5 mEq/L. This concentration induces only a slight positive balance of 91 mg per dialysis of 4 hours on a standard Kiil [41] and unlike a DCa of 6.0 mg/dl [41] does not induce a decrease in ionised calcium.

**Dialysate magnesium (DMg)** The optimal DMg has not been studied as critically as DCa. The most commonly used concentrations, 1.2 and 1.8 mg/dl, are associated with elevated predialysis PMg of 2.0 - 4.0 mg/dl [1,2,3]. The use of a DMg of 0.6 mg/dl may be preferable, since hypermagnesaemia has deleterious effects on bone crystal maturation and on visceral calcification. A recent study suggests that this DMg has in fact a beneficial effect on bone [44]. In contrast, Pletka recommended the use of a DMg of 2.4 mg/dl because it decreased PPTH more than a DMg of 0.6 mg. However, Pletka was using a DCa of 5.4 mg/dl and Ritz who has used a DCa of 7.0 mg/dl could not confirm this effect [1]. Provided DCa is adequate, there is no reason to use a high DMg.

**Phosphate-enriched dialysate** Phosphate depletion can occur in patients on chronic haemodialysis even when no Al(OH)₃ is taken [36]. This depletion, characterised by predialysis PP0₄ less than 3.0 mg/dl and postdialysis PP0₄ less than 2.5 mg/L, is relatively frequent in England and can lead to pure osteomalacia not responsive to vitamin D therapy and eventually associated with dialysis dementia [36]. In hypophosphataemic patients, we suggest that dietary PO₄ be increased by a higher intake in protein and dairy products and the use of vitamin D. When these measures are not sufficient, it may then be justified to use a phosphate enriched dialysate according to the technique of Pierides. This has led to improvement in some cases of both osteomalacia and dialysis dementia [36].

**Purity of water** The water used for the preparation of dialysate is frequently pure tap water when the concentration of calcium is low, or softened water. The softener does not affect the concentration of trace elements. The role of these trace elements was first suggested by Posen of Ottawa [1] who found a decrease in the incidence of osteomalacia after substitution of deionised or reverse osmosed water for softened water. Experience was similar in Newcastle upon Tyne, another centre with a high incidence of pure osteomalacia. This osteomalacia is characterised by the absence of hyperparathyroidism (normal PPTH), normal alkaline phosphatase, normal plasma concentration of 25 OH D, association with a severe myopathy and dialysis dementia, and a poor response to 1α hydroxylated derivatives of vitamin D. This complex syndrome was improved with phosphate-enriched dialysis in only a few patients with hypophosphataemia [36]. A recent report showed that the incidence of osteomalacia was reduced in the patients dialysed against deionised water (15%) compared with those dialysed against softened water from the same source (70%) [5]. The fact that the patients with osteomalacia and dementia have the higher concentrations
of aluminium in their dialysate, in their blood and in the grey matter of their brain, strongly suggests that aluminium absorption from the dialysate causes osteomalacia and encephalopathy. The toxicity of other unknown trace elements in the water cannot be excluded. Fluoride has also been incriminated, but Oreopoulos has shown in a controlled trial that, at a concentration of 1 mg/L, fluoride does not induce significant osteomalacia after 1 year, but increases osteosclerosis [cited in 1]. Because of these potential hazards, use of deionisation or reverse osmosis to treat dialysate water is advised, and are mandatory in areas with a high aluminium content in the water (greater than 50 µg/L). Similarly, we would recommend this water treatment when fluoride concentration is greater than 500 µg/L. Contamination by trace metals should be avoided on the way to the patient (no aluminium pipes or heater), verified by estimating aluminium and fluoride in the dialysate.

Schedule and duration of dialysis These factors obviously affect the pathophysiology of renal osteodystrophy, since they determine the calcium and phosphate balance as well as the acid-base status. Bonomini has shown that 3 dialyses of 4 hours per week did not prevent increase in resorption surface whereas 5 dialyses of 2 hours did. However, for practical reasons ‘daily’ dialysis is usually impossible and we would recommend at least 3 times 4 hours a week, provided measures are taken between dialyses to prevent negative calcium balance and hyperphosphataemia.

Heparin and dialysis membranes Chronic heparin administration in large doses has been shown to induce osteoporosis. Since dialysed patients receive heparin regularly, this factor may contribute to their bone disease. Minimal heparinisation is therefore recommended. We have shown that polyacrylonitrile membrane was able to clear PTH₇₀₀₀ whereas cuprophane was unable to do so. Although PTH decreased by 50% during each haemodialysis with PAN membrane, predialysis PTH were not different after one month using cuprophane membrane [45].

Optimal haemodialysis conditions to prevent osteodystrophy

1. the water should be treated either by deionisation or by reverse osmosis. The DCa should be 6.5 when vitamin D is given or 7.0 mg/dl when no vitamin D therapy is given. Optimal DMg may be 0.6 mg/dl. No phosphate should be added, except when hypophosphataemia cannot be corrected by the diet and vitamin D therapy, which is exceptional
2. the schedule should be at least 4 - 6 hours 3 times a week, regardless of the membrane
3. between dialyses, the diet should be restricted only in dairy products, but protein intake should be around 1 g/kg
4. calcium supplements should be given to bring Ca intake to 1.5 g of elemental calcium per day when vitamin D is given and a DCa of 6.5 - 7 mg/dl is used. Larger supplements may be given only when no vitamin D is given.
5. enough phosphate binders should be given to keep predialysis phosphate
to 4.5 ± .5mg/dl. This control of hyperphosphataemia is especially critical when
duration of dialysis is short (4 hours) and when vitamin D is administered. We
have observed that when the duration of dialysis is shortened, but Al (OH)₃
dose is not increased, PPO₄ increases together with an increase in osteoclast
counts, and osteoclastic resorption surface. Serum aluminium must be monitor-
ed yearly or even more frequently in areas with high water aluminium and in
patients taking huge doses of PO₄ binders. When serum aluminium is above
200 µg/L, phosphate binders should be reduced, dairy products more restricted
and the duration of dialysis increased, and the water appropriately treated.

(6) Vitamin D therapy is advised as before dialysis, with the same recom-
manded dosage and monitoring. It is recommended without reservation in all
children and adults with radiographic abnormalities. When no radiographic
abnormalities are present in adults, vitamin D therapy is recommended only
with extreme caution. One still has to await further clinical trials to see whether
preventive treatment with vitamin D is better than the approach proposed by
the Mayo Clinic in 1974 (see above). Increased difficulties in controlling hyper-
phosphataemia when vitamin D is used may counterbalance the beneficial effects.

Renal Osteodystrophy and Peritoneal Dialysis (PD)

Evaluation of renal osteodystrophy during chronic peritoneal dialysis has not
been widely reported. We are aware only of the study of Oreopoulos [46] show-
ing that 22 hours of PD twice a week improved osteomalacia, while 6 hours
of haemodialysis 3 times a week increased it. This difference may have been due
to the higher calcium concentration (7.0 vs 6.0 mg/dl) and to the use of disti-
illed water in PD, whereas softened water with fluoride and probably aluminium
was used for the haemodialysis dialysate. It is however possible that PD
alone is able to decrease the uraemic calcification-inhibiting factor of Yendt,
which may be a polypeptide.

However, intermittent chronic PD seems to be less able to control hyper-
phosphataemia and osteitis fibrosa. The new technique of continuous chronic
peritoneal dialysis proposed by Oreopoulos could represent an advance.

The same extradialytic therapeutic measures are recommended as for patients
on chronic haemodialysis.

Renal Osteodystrophy and Haemofiltration

Haemofiltration is the ultrafiltration of about 1 litre of plasma/per kg of body
weight/per week in 3 procedures, and replacement of fluid lost by a substitution
fluid. The volume of this substitution fluid is equal to the quantity of ultrafil-
trate (QUF) minus the body weight loss (ΔBW), plus about one litre due to the
priming of the tubes and the oral liquid taken during the procedure. We have
shown [47] that in order to prevent negative calcium balance during this pro-
dure, the concentration of calcium in the substitution fluid (RCa) should be
at least equal to the ratio

\[ RCa = \frac{UFCA \times UFQ}{UFQ - (\Delta BW + 1)} \]

(where UFCA is the patient ultrafiltrable calcium)

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In practice, with a UFCa equal to 6.0 mg/dl, a UFQ of 20 litres and a ΔBW of 2 kg, RCa should be at least of 7.0 mg/dl. Therefore, we recommend the routine use of a RCa of 8.0 mg/dl.

The prevention of negative calcium balance is critical for the long term control of hyperparathyroidism. This latter is however no better achieved with haemofiltration than with haemodialysis with PAN membrane. In contrast to Fuchs [48], we have not found that the dosage of PO₄ binders could be reduced with this technique.

In agreement with Schaefer [49], we have found that haemofiltration could remove significant amounts of PTH, but we have never found higher concentrations of PTH in the ultrafiltrate than in the plasma.

We recommend that between the haemofiltration procedures, the same therapeutic measures as those used for patients treated with haemodialysis be used.

Renal Osteodystrophy and Surgical Parathyroidectomy

The incidence of surgical parathyroidectomy (PTX) varies widely from one centre to the other. This is most likely due to differences in dialysis conditions. We hope that the above therapeutic measures, which may induce a medical parathyroidectomy, will further limit these indications.

Indications

Surgical parathyroidectomy is indicated when medical PTX has failed to prevent or cure overt osteitis fibrosa, i.e. when phosphate binders, 3 g of CaCO₃, vitamin D therapy and at least 3 times 4 - 6 hours of dialysis with the optimal technical conditions, are associated with non regression of the subperiosteal resorption and the metastatic calcifications, with a persistent hypercalcaemia (> 10.5 mg/dl) and/or a persistent hyperphosphatemia (> 6.0 mg/dl), despite a low maintenance dose of vitamin D (100 µg of DHT, 25 µg of 25 OH D₃, 0.5 µg of 1α OH D₃, 0.25 µg of 1α,25 (OH)₂ D₃). Hypercalcaemic, unrelated diseases like myeloma, sarcoidosis, etc., should of course be eliminated. Similarly osteomalacia with no increase in PiPTH and normal serum alkaline phosphatase should be eliminated on radiographical and possibly on histological evidence, since it is recognised that in such situations, vitamin D metabolites are ineffective and can induce hypercalcaemia. PTX may only worsen the osteomalacia and this osteomalacia can only be improved by elimination of water toxin. Hyperparathyroidism is usually due to diffuse hyperplasia of the chief cells of the 4 glands and more rarely to a true adenoma. The reason for this apparent autonomy of the glands is mainly related to their increased mass, since tissue culture experiments have shown that cells of these 'autonomous' glands have a secretion rate responsive to various stimuli but produce, as do the cells of normal glands, a basal non-suppressible secretion.

More rarely, PTX may be necessary for severe pruritus not altered by increasing dialysis times or by giving cholestyramine or antihistamine drugs. Sometimes, PTX has to be considered urgently because of skin ulceration and tissue necrosis due to vascular calcification and calciphylaxis. Although anaemia
may be improved by PTX, it is not an indication per se for PTX.

**Surgical Procedures**

In order to prevent post PTX hypocalcaemia and tetany, it is advisable to give 1α derivatives of vitamin D₃ 48 hours before surgery (4 μg of 1α OH D₃ or 2 μg of 1α,25 (OH)₂ D₃). Because of the hazard of hypoparathyroidism and of post PTX osteomalacia, total parathyroidectomy should be abandoned. Total parathyroidectomy with transplantation of 20 pieces of 1 x 1 mm of parathyroid tissue into the forearm musculature has been recommended by Wells to treat secondary renal hyperparathyroidism [50]. The main justification for this procedure is that if severe hyperparathyroidism recurs, it will be much more easily corrected by taking out a few pieces of parathyroid graft from the forearm than by a further neck exploration. However, this operation may be complicated by necrosis of the transplant and although other pieces of parathyroid gland may be kept in the freezer, their viability has been proved in man in only one case.

We recommend at present the safer classical subtotal parathyroidectomy taking out 3½ parathyroid glands. When the appropriate measures of medical parathyroidectomy are taken, the risk of recurrent hyperparathyroidism seems to us negligible.

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Open Discussion

CHAIRMAN May I congratulate you for this truly brilliant task of summarising the treatment of renal osteodystrophy in so few minutes. You were successful in steering clear of the Scylla of simplification and the Charybdis of confusing complexity. I am sure there are some questions and not everyone will agree with all the points you made.

KERR (Newcastle) I was interested in your data on the different effect of ‘25’ and ‘1,25’ on mineralisation, but of course the change in mineralisation must depend upon the base line from which you are working and certainly in our experience of only four patients on 1α, three have pushed their mineralisation front from highly abnormal to virtually normal levels with 1α OH vitamin D3. I wonder, therefore, from what level of mineralisation front you were starting in the patients whom you treated with 1α.

FOURNIER This study was done after appropriate matching of the two groups, and in the two groups the initial mineralisation front was around 35%.

KANIS (Oxford) I was interested to hear you advocating, not widely but certainly approaching the position where you envisage prophylaxis of renal bone disease with vitamin D-like compounds. It seems a very attractive hypothesis in the sense that you can reverse some established hyperparathyroid bone disease with vitamin D. But it is a different question altogether as to whether one can prevent its inception and one wonders, especially when one is treating patients with osteitis fibrosa, whether in fact one is doing anything to the parathyroid gland at all; whether one is causing parathyroid involution even though one is causing parathyroid hormone suppression. There are the occasional observations that patients treated with long term 1α may develop so-called autonomous or tertiary hyperparathyroidism and become intolerant of 1α hydroxycholecalciferol and that on withdrawal of treatment they are in a tertiary hyperparathyroid-like state, though I don’t like to use that term. It seems just possible that if we are going to use the vitamin D metabolite prophylactically on a wide scale before we have adequate knowledge, we might in fact be doing some harm to our patients.

FOURNIER You say that with 1α you may in some cases induce more frequent autonomy of the parathyroids.

KANIS I know that Robin Whinney from Edinburgh has seen a couple of cases
like this and we have as well. It is not a common response, but it raises the possibility although we are decreasing the secretion of parathyroid hormone, and after all we have only studied these patients since about 1973 or 1974 so we have not got a lot of experience yet. We have no evidence whatsoever to suggest that the parathyroid glands themselves are getting smaller; one hopes they are but they could even be getting bigger - one does not know.