Bone Disease in Kidney Failure:

Diagnosis and Management

Medical Grand Rounds

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Several recent therapeutic advances have improved the life of the patient with end stage renal disease (ESRD). High efficiency and high flux hemodialyzer membranes have shortened the time required to adequately dialyze and recombinant erythropoietin has all but eliminated anemia as a major cause of morbidity, but the problem of renal osteodystrophy remains. This Grand Rounds will examine the spectrum of bone and joint disease in the patient with ESRD. The diagnostic and therapeutic strategies currently being tried in the management of these disorders will be discussed.

Table 1 lists the types of bone disease that afflict the dialysis patient.

Table 1

Uremic Bone Diseases

Osteitis fibrosa
Osteomalacia
Mixed renal osteodystrophy
Aplastic bone disease
Dialysis related amyloidosis

In **osteitis fibrosa**, the characteristic histologic lesion of secondary hyperparathyroidism, the bone is very active as measured by a high bone formation rate, with many osteoclasts and osteoblasts covering a widened osteoid seam; a variable degree of peritrabecular fibrosis is present. In contrast, **osteomalacia**, associated with vitamin D deficiency and/or aluminum intoxication, is characterized by bone inactivity as measured by a low bone formation rate, decreased osteoclasts and osteoblasts, and a very wide osteoid seam. **Mixed renal osteodystrophy** represents a composite of the these two processes and is seen when secondary hyperparathyroidism and vitamin D deficiency develop at the same time. It sometimes occurs in patients developing aluminum toxicity on a background of prior osteitis fibrosa. **Aplastic bone disease** is characterized by the near absence of new bone formation and reduced bone volume. There are very few areas of widened osteoid. There is a conspicuous absence of osteoclasts or osteoblasts. This lesion often occurs in the presence of excessive aluminum but may be seen with excessive suppression of parathyroid hormone. **Dialysis related amyloidosis** is a newly recognized member of the family of bone diseases that affect hemodialysis patients. Its most serious clinical manifestation is accumulation of amyloid substance within bone with the eventual development of pathological fractures. However, its clinical presentation more often depends

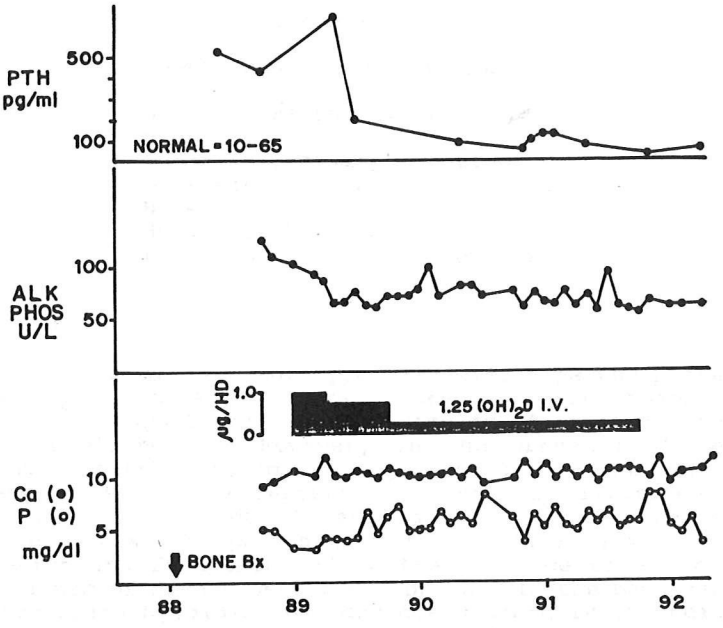
on its propensity to invade synovial membranes causing a variety of articular and periarticular syndromes, most notably carpal tunnel syndrome.

The following case descriptions are of patients currently being dialyzed at the Dallas VAMC. They will be used to highlight these bone disorders and serve as points of departure to briefly discuss diagnostic and management aspects of these problems.

Case 1. (Figure 1)

J.B. is a 56 year old white male with ESRD secondary to chronic glomerulonephritis. He has been on chronic hemodialysis since December, 1978, except for an eight month period on CAPD in 1982. Cadaveric renal transplants were acutely rejected in 1981 and 1984. Although bone x-rays were normal, serum PTH levels were very high, and an iliac crest bone biopsy in January 1988 showed severe

Fig 1



osteitis fibrosa and severe osteoporosis; there was no evidence of aluminum disease. Intravenous 1,25 (OH)2 D

was begun in Jan 1989 at a dose of 1 mcg at the end of each hemodialysis treatment and was gradually tapered to 0.25 mcg and discontinued in October of 1991 when the parathyroid hormone level fell to normal. In December, 1991, he complained of shoulder pain. Shoulder x-rays and MRI were negative. Dialysate calcium was reduced to 2.5 meq/L in January, 1992. Although he previously required aluminum containing antacids, currently the patient requires only calcium acetate, 3 grams with meals, for phosphate control. Serum calcium is in the high normal range. He continues to have mild bilateral shoulder pains, but analgesics are not required. A repeat bone biopsy is scheduled.

Osteitis fibrosa. Overt secondary hyperparathyroidism is characterized by musculoskeletal symptoms, a high PTH level, radiographic evidence of subperiosteal reabsorption, and bone biopsy evidence of osteitis fibrosa (Table 2). In addition to a high PTH, the other biochemical markers of secondary

Table 2

Uremic Hyperparathyroidism

Musculoskeletal symptoms
High PTH
Subperiosteal reabsorption
Osteitis fibrosa
Hypercalcemia
Hyperphosphatemia
Elevated alkaline phosphatase

hyperparathyroidism may include hypercalcemia, hyperphosphatemia, and an elevated alkaline phosphatase. Hyperphosphatemia unresponsive to phosphate binding antacids is often attributed to patient non-compliance. However, in the presence of severe secondary hyperparathyroidism, a significant fraction of this hyperphosphatemia probably represents phosphorus liberated from bone under the influence of PTH and is not under the patient's control. A high alkaline phosphatase value indicates very active bone resorption and formation and in the presence of a high PTH value is a marker of severe osteitis fibrosa. In the past decade, secondary hyperparathyroidism has decreased steadily in incidence due in large part to better phosphorus control and the use of vitamin D analogues.

Phosphate Control. The concentration of serum ionized calcium is the primary determinant controlling the secretion of PTH.

Hyperphosphatemia promotes secondary hyperparathyroidism by producing hypocalcemia and skeletal resistance to the effect of PTH (1,2). The prevention of secondary hyperparathyroidism through control of serum phosphorus is central to the prevention of uremic osteodystrophy (Table 3). Secondary

Table 3

Effects of Hyperphosphatemia

Hypocalcemia
Elevated PTH
Skeletal resistance to PTH
Decreased renal production of 1,25 $(OH)_2$ D

hyperparathyroidism in the patient with chronic renal failure develops long before dialysis is initiated. As the glomerular filtration rate falls, phosphorus excretion per nephron rises as the result of progressively greater secretion of parathyroid hormone (3). Through this mechanism, phosphorus levels remain normal until the glomerular filtration rate has fallen to 30 ml/min. As filtration rate falls, renal production of 1,25 (OH)2 D declines progressively. Hyperphosphatemia further reduces 1,25 (OH)2 D formation probably by impairing the enzyme 1-α hydroxylase. With severe renal failure, PTH levels rise higher and calcitriol falls further. Control of serum phosphorus as this point is important primarily as a mechanism for suppressing PTH levels; it has little effect to further stimulate the low 1,25 (OH)2 D level (Table 4). In the

Table 4

Measures For Control of Hyperphosphatemia

1. Reduce Unnecessary Dietary Phosphorus
   (e.g. dairy products)
2. Encourage High Protein Foods (meats, eggs)
3. Dialysis
4. Phosphate Binders

predialysis and dialysis patient, dietary phosphorus restriction is necessary. However, a marked reduction in dietary phosphorus can only be accomplished by severely restricting protein intake. Since a large fraction of the dialysis population is frankly malnourished or borderline malnourished, protein supplementation rather than restriction is required. Thus, the present goal of dietary therapy is to restrict intake of unnecessary dietary phosphorus (dairy products, certain vegetables, colas) while encouraging the intake of high protein foods (meats, eggs). The dietary phosphorus load from a high protein diet can be dealt with using dialysis and phosphate binders. The dialysis procedure is limited in its ability to remove phosphorus, not because hemodialysis membranes

are inefficient, but because there is a slow efflux of phosphorus from the intracellular to the extracellular space where the dialysis procedure is taking place (4). Thus, lengthening dialysis or using a larger, high efficiency dialyzer is unlikely to yield significantly better phosphorus control. However, the recent trend to shortened dialysis and the use of recombinant erythropoietin which through an increase in red cell mass decreases the relative amount of plasma exposed to the dialysis process are factors which can decrease the dialytic removal of phosphorus (5). Aluminum binding antacids were the mainstay for phosphate control for many years and continue to be the most effective binders of phosphorus. Unfortunately, aluminum containing antacids have proved toxic and even fatal to many dialysis patients and their use should now be restricted to patients with the most refractory hyperphosphatemia and only for short periods of time.

Calcium containing phosphate binders. Calcium containing antacids have largely replaced aluminum containing antacids as the first choice phosphate binder for dialysis patients, but they are less effective (Table 5). In early studies using calcium

Table 5

Calcium Containing Binders

1. Safer, But Less Effective As Binders
2. Hypercalcemia
3. Calcium Carbonate
4. Calcium Acetate
5. Calcium Citrate

carbonate, good control of serum phosphorus could be achieved in approximately 70% of patient, but 30% required the addition of aluminum containing agents to control phosphorus (6). Hypercalcemia has been the limiting factor which has made necessary the addition of some aluminum binders. Calcium acetate has recently been added as another effective phosphorus binder with the apparent advantage that it binds phosphorus but with a lower dose of elemental calcium (7,8,9). Mai et al (7) demonstrated that calcium acetate binds twice the amount of phosphorus per amount of calcium absorbed. The disadvantages of calcium acetate over calcium carbonate have been that the volume of medication is not decreased, since the amount of calcium per tablet is less (25%) compared with calcium carbonate (40%), and, for some patients, there is an unpleasant aftertaste. Hypercalcemia is also a problem with calcium acetate (8,9). However, lowering the **dialysate calcium** concentration has safely allowed the use of larger doses of calcium (10). Hou et al (4) evaluated in a 4 hour dialysis session the acute effects of varying dialysate calcium concentration and noted that patients gained calcium (879 mg) when dialyzed against a 1.75 mmol/L bath, had no net calcium flux with a 1.25 mmol/L bath, and lost calcium (231 mg) with a 0.75 mmol/L bath. The

combination of calcium containing antacids and a low calcium dialysate should reduce the number of patients who still require aluminum binders to a very small number (Table 6). Calcium citrate has been proposed as another non aluminum containing

Table 6

Dialysate Calcium

-Traditionally 3.25-3.5 meq/L
-Currently lower, e.g. 2.5 meq/L

phosphorus binder (11). However, the citrate ion has the serious drawback of enhancing aluminum absorption and may induce an acute neurotoxicity syndrome and the rapid onset of symptomatic osteomalacia (12,13,14). This effect appears to be mediated by increased absorption of aluminum through a citrate-induced opening of cellular tight junctions in the proximal small bowel (15). Citrate is the alkalinizing agent found in Shohl's solution and commonly used in patients with renal failure. Since aluminum is found in many foods and medications besides aluminum containing antacids (e.g. buffered aspirin, sucralfate), the use of Shohl's solution should be curtailed in this population (12).

1,25 $(OH)_2$ D in dialysis patients. Deficiency of 1,25 (OH)2 D may contribute to the development of secondary hyperparathyroidism (Table 7). 1,25 (OH)2 D receptors are abundant

Table 7

1,25 $(OH)_2$ D in Dialysis

1. Deficiency Causes Secondary Hyperparathyroidism
2. 1,25 $(OH)_2$ D Receptors on Parathyroid Cells
3. Set Point For Calcium Increased in Secondary Hyperparathyroidism
4. 1,25 $(OH)_2$ D Decreases Calcium Set Point
5. 1,25 $(OH)_2$ D Decreases PTH
6. 1,25 $(OH)_2$ D Lowers Bone Formation Rate
7. Intravenous or Oral Use

on the parathyroid gland, and studies of parathyroid cells in culture and in vivo show a reduction of mRNA for preproparathyroid hormone when 1,25 (OH)2 D is added to the culture (16,17,18). The set point for calcium, i.e. the serum calcium which will suppress the production of PTH by the parathyroid gland, is increased in secondary hyperparathyroidism (19,20). The clinical corollary of this observation is that a higher than normal serum calcium (i.e. 10.5-11.5 mg/dl) may be required to suppress PTH levels in secondary hyperparathyroidism. This may be difficult to achieve in many dialysis patients because of the presence of hyperphosphatemia and the need to keep the calcium x phosphorus

product below 70 to prevent the development of metastatic calcifications. The therapeutic use of 1,25 (OH)2 D appears to be a way out of this dilemma, since it reduces the calcium set point for PTH release. Long-term, intravenous 1,25 (OH)2 D (21-24) decreases PTH levels and improves the histologic abnormalities of renal osteodystrophy while producing little hypercalcemia. Andress et al (23) gave intravenous 1,25 (OH)2 D, 1-2.5 μg three times weekly during dialysis for 11 months and noted a decline in bone formation rate, a reduction in osteoblastic osteoid, and reduced marrow fibrosis (Table 8). The effect of 1,25 (OH)2 D to lower bone formation rate appears to be due to its effect to lower PTH (21,22) which in turn decreases the stimulus for osteoblastic proliferation. There may also be a direct inhibitory effect of 1,25 (OH)2 D on the number and function of differentiated osteoblasts (25,26).

Table 8

Bone Indices With Intravenous 1,25 (OH)2 D Treatment

	Before	After
Bone Formation Rate $\mu m^2/mm^2/day$	1642±277	676±106
Osteoblastic-Osteoid Surface μm	18±3	9±2
Marrow Fibrosis (% area)	6.2±1.7	3.5±1.3

Ref. (23)

Rodriquez et al (27) demonstrated that long-term, intravenous 1,25 (OH)2 D treatment (42 weeks) decreased the sensitivity of the parathyroid gland to changes in ionized calcium, although the set point for calcium (i.e. serum calcium concentration required to reduce PTH by 50%) did not change. They suggested that the change in slope of the PTH/calcium relationship was a better index of 1,25 (OH)2 D action on the parathyroid gland than the change in set point used by other investigators (21,22). The absolute degree of suppression of PTH by 1,25 (OH)2 D appears to be proportional to the magnitude of the serum level prior to therapy (27), even after long-term treatment (27). This raises the important question of whether 1,25 (OH)2 D suppression of the parathyroid gland is capable of causing involution of the gland or merely a controlled suppression of the hypertrophied gland's ability to produced PTH. At least with short term treatment, (i.e. 4 months), interruption of 1,25 (OH)2 D therapy leads to a relatively rapid return of PTH levels to baseline (21).

Oral 1,25 (OH)2 D may also be used effectively in dialysis patients to treat uremic hyperparathyroidism. Quarles et al (28) gave an average dose of 0.6 μg of 1,25 (OH)2 D in a divided daily dose together with oral calcium carbonate to 8 hemodialysis

patients for nine months and noted a marked suppression of serum PTH without the development of hypercalcemia. Oral 1,25 $(OH)_2$ D can also be given in a "pulse" fashion following dialysis (29). A dose of 6 μg orally, 10 times the usual daily oral dose, at the end of dialysis twice weekly leads to marked suppression of PTH and alkaline phosphatase activity without development of hypercalcemia.

In using 1,25 (OH)2 D to lower the bone formation rate, there is a risk that some patients will develop aluminum related bone disease. Andress et al (23) have recommended that prolonged or complete suppression of the parathyroid gland be avoided, since abnormally low bone formation rates enhance the deposition of aluminum on the mineralization front.

1,25 (OH)2 D in pre-dialysis patients. The exact role 1,25 $(OH)_2D$ in the management of the predialysis patient is still to be defined. There were early concerns that 1,25 (OH)2 D might hasten the decline of the remaining renal function by causing hypercalcemia, hyperphosphatemia, and hypercalciuria. Reports to date indicate either a reversible decline (30) or no decline in renal function (31). The mechanism of the reversible decline might be due to impaired tubular secretion of creatinine and thus be functional rather than a real loss of filtration. Nevertheless, it seems prudent to reserve this form of therapy in the predialysis patient to those patients demonstrating severe and symptomatic, biopsy proven secondary hyperparathyroidism characterized by hypocalcemia and an elevated alkaline phosphatase.

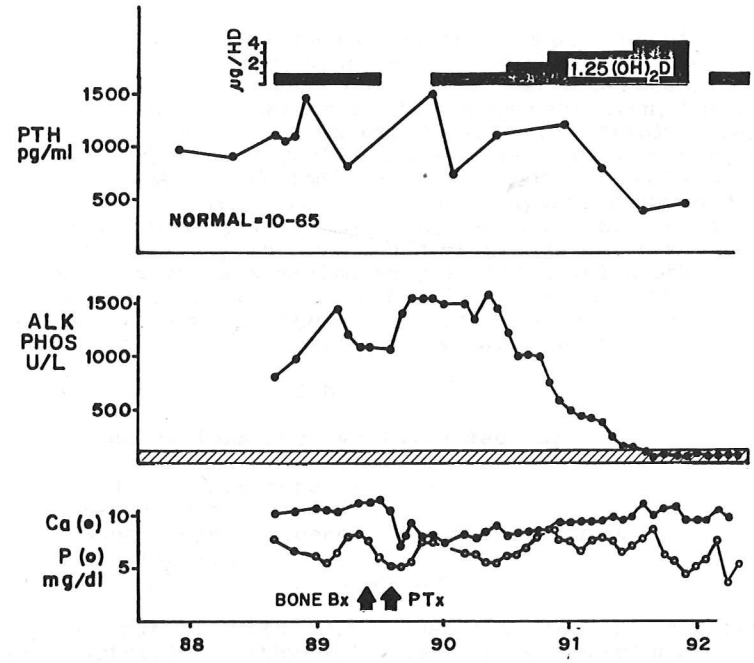
Clinical issues in Case #1. 1. Bone biopsy was performed because of the high PTH level. Note that at the time of the biopsy serum phosphorus control was excellent at 5 mg/dl, but serum calcium was in the low range of normal at 9.0 mg/dl and probably the stimulus for the elevated PTH level. Alkaline phosphatase was in the upper normal range. Although serum 1,25 (OH)2 D was not measured, it is likely that it was low since with institution of vitamin D therapy, there was a marked fall in PTH and alkaline phosphatase. Thus, two factors were involved in the suppression of PTH: a) a rise in serum calcium brought on by enhanced gut absorption of calcium by vitamin D, and b) the rise in serum 1,25 (OH)2 D itself which suppressed the release of PTH from the parathyroid gland. 2. Serum phosphorus also rose with continued vitamin D therapy, an effect mediated by vitamin D enhancement of gut phosphate absorption. 3. The current concern is that the bone pain the patient began experiencing in late 1991 may be due to the development of aluminum related osteomalacia or aplastic bone disease, both potential consequences of oversuppression of the parathyroid gland. A bone biopsy is planned to assist the planning of future therapy.

Case 2 (Figure 2)

W.N. is a 77 year black male with end-stage renal disease resulting from hypertension. He began hemodialysis April 22, 1987. A metabolic bone survey in

March, 1989, showed generalized bone demineralization and a "rugger jersey" spine. Parathyroid hormone and serum alkaline phosphatase levels were elevated greater than 10 times the normal level. An iliac crest bone biopsy on June 22, 1989, showed "severe osteitis fibrosa". Phosphate control with aluminum containing antacids and a brief trial with low dose intravenous and oral 1,25 (OH)2 D therapy caused no improvement. On July 10, 1989, a total parathyroidectomy and autotransplantation of parathyroid tissue into the left forearm brachioradialis muscle were performed. Postoperatively, serum calcium fell to 7 mg/dl, but within a few days plateaued at 8 mg/dl. He was discharged on oral calcitriol 0.25 mcg daily, calcium carbonate 750 mg b.i.d., and aluminum

Fig 2



carbonate 3 capsules t.i.d. After surgery, parathyroid hormone and alkaline phosphatase remained elevated. In March 1990, surgical reexploration was considered, but a parathyroid scan failed to identify retained tissue in the neck. Venous PTH samples from the right and left

arms failed to show a gradient suggesting, but not proving, that the source of the hormone was not the transplanted material. A "medical parathyroidectomy" was considered the best approach. Intravenous 1,25 (OH)2 D was begun at a dose of 1 μg following each hemodialysis treatment, and advanced to 4 μg over the next one and a half years. By the end of 1991, there was a 95% reduction in alkaline phosphatase and a 75% reduction in parathyroid hormone. Serum calcium briefly rose to greater than 11 mg/dl in late 1991 and 1,25 (OH)2 D3 was stopped for 2 months and then restarted at 1 μg per hemodialysis treatment. Prior to November 1991, dialysate calcium was 3.5 meq/L. It was then reduced to 3.0 meq/L and further lowered to 2.5 meq/L in January, 1992, to permit the continued, combined use of 1,25 $(OH)_2$ D and calcium containing phosphate binders and thus minimize the risk of hypercalcemia.

Parathyroidectomy. The necessity to perform parathyroidectomy for patients with secondary hyperparathyroidism has decreased significantly in the past decade due to a better understanding of measures which can suppress parathyroid hormone secretion, the most important being 1,25 (OH)2 D. However, despite calcitriol therapy, severe secondary hyperparathyroidism sometime requires surgical parathyroidectomy. A normal individual has 4 parathyroid glands each weighing 30-40 mg; in secondary hyperparathyroidism, individual hyperplastic glands may weigh as much as 2-3 grams. There is great variability in the number of glands which are found at surgery, some individuals having only 3 glands while other have 6 or more. This may explain why there is a significant failure rate for patients who undergo total parathyroidectomy. The indications for surgical parathyroidectomy are shown on Table 9.

Table 9

Indications for Parathyroidectomy

Radiographic bone erosions
Markedly elevated PTH
Bone biopsy evidence of osteitis fibrosa
Calciphylaxis
Unresponsive hyperphosphatemia

Total parathyroidectomy with autotransplantation is currently favored over subtotal parathyroidectomy since reexploration in patients with subtotal parathyroidectomy is associated with increased morbidity and mortality. The incidence of recurrent hyperparathyroidism is similar for both operations ranging from 6-13% (32,33). The problem of how to deal with recurrent disease as in this patient is a difficult one (Table 10). The source of the PTH is often difficult to determine despite the

Table 10

Problems With Parathyroidectomy

1. Incomplete operation
2. Al-induced osteomalacia
3. Hypocalcemia, hypophosphatemia
   -"hungry bone syndrome"

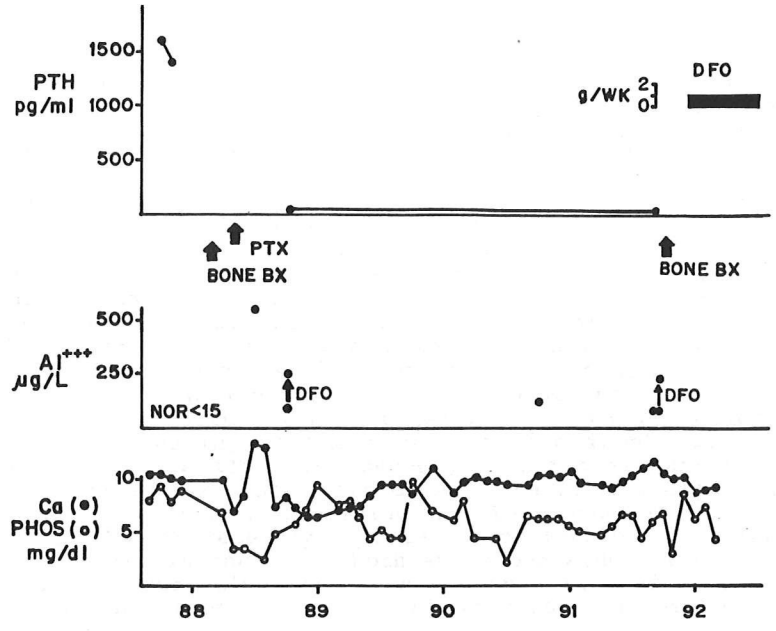
apparent ease of testing for PTH secretion from the autotransplant by sampling the venous effluent of the arms. Even using total parathyroidectomy without autotransplantation, few patients are left with undetectable levels of PTH (32), suggesting that small residual areas of parathyroid tissue remain. Because of the risk of aluminum induced osteomalacia occurring after parathyroidectomy (34), autotransplantation will continue to be the favored operation. The characteristic biochemical changes in the post operative period are a marked decline in serum calcium and phosphorus, manifestations of the "hungry bone syndrome." This can be reduced substantially if the patient is given 1,25 (OH)2 D, 0.5-1.0 μg/day for several days before surgery. Oral calcium and relatively high doses of calcitriol, 1-2 μg/day, are continued for several weeks into the post operative period, or until serum calcium can be controlled with lower doses of calcitriol and oral calcium.

Clinical issues in Case #2. 1. The fall in serum calcium and serum phosphorus postoperatively were relatively modest, the first indication that the operation was incomplete. This was confirmed by the persistently high PTH levels. 2. Except for a persistently elevated PTH, intravenous 1,25 $(OH)_2$ D has normalized the biochemical markers of secondary hyperparathyroidism. Serum phosphorus can now be controlled with calcium containing phosphate binders alone.

Case 3 (Figure 3)

O.S. is a 66 year old white male with ESRD secondary to chronic glomerulonephritis. Prior to starting hemodialysis on 2/1/84, he took aluminum containing antacids in large doses to control a high serum phosphorus. In 1986, he was noted to have an elevated serum aluminum level and was treated for a few months with desferoxamine chelation therapy, 2 grams weekly. In 1987, he began complaining of generalized bone pains, especially in the shoulders and back, but also the neck and knees. Uncontrolled hyperphosphatemia, bone x-rays, and laboratory studies were consistent with secondary

Fig 3



hyperparathyroidism. An iliac crest bone biopsy on Feb 2, 1988 showed severe osteitis fibrosa and no staining for aluminum. On May 20, 1988, subtotal parathyroidectomy and autotransplantation of one gland to his forearm were performed. Oral calcium supplements and oral 1,25 (OH)2 D were prescribed but within a few months caused marked hypercalcemia, 13.5 mg/dl, and the dose was reduced. Over the next two years serum PTH levels remained quite low, but a high serum phosphorus required large doses of aluminum containing antacids. DFO stimulation tests performed in October, 1988, (pre Al 51 µg/L, post 245 µg/L) and September, 1991, (pre Al 68 µg/L, post 228 µg/L) indicated the presence of a significant aluminum load. During this time the patient regularly complained of bone pain, especially of the shoulders and back. He also had proximal muscle weakness manifested by an inability to rise from a squat. Nonsteroidal antiinflammatory agents were only partially helpful. Approximately 6 weeks following the second DFO stimulation, and during a period of reduced and less efficient dialysis, the patient developed an acute dementia characterized by disorientation, an inability to recognize family members and dialysis staff. In addition he had myoclonic jerking, intention tremors, and dysarthria. Lumbar puncture and CT scan were negative. EEG showing moderate to severe generalized slowing consistent with Al encephalopathy. The diagnosis was

presumed to be aluminum encephalopathy and DFO chelation was begun in conjunction with a change to a high-flux dialyzer membrane (Fresinius F80) capable of very efficiently removing the aluminum-DFO chelate. Because of declining nutrition secondary to the dementia and the requirement for intensive nursing, plans were initiated for temporary nursing home placement. However, within five days of beginning DFO, there was rapid clearing of the dementia such that he was considered back to baseline and discharged to home. In addition to the complete clearing of the mental confusion, in the following months the patient noted almost complete resolution of the chronic bone pain. An iliac crest bone biopsy performed Jan 13, 1992 showed that the predominant lesion was now osteomalacia with a marked reduction in bone formation; aluminum staining of the mineralization front was now present (Table 11). The serum phosphorus is currently well controlled using exclusively calcium containing antacids. Dialysate calcium has been reduced to 2.5 meq/L. He has recently reported mild blurring of vision and ringing in the ears; both are known side effects of DFO. DFO chelation continues but at a reduced dose of 0.5 grams intramuscular the night before the mid-week dialysis.

Table 11

Bone Biopsy Results, Patient 3

	2/3/88	1/13/92	Normal
Osteoid surface %	61.9±5.8	52.9±0	16±6
Tetracycline surf %	66.8±1.0	5.64±0	13±4
Mineralization rate, μ/d	1.3±0.4	0.3±0	0.7±1
Osteoclasts/mm	17.2±0.8	1.09±0	0.3±0.3
Aluminum	neg	pos	neg

Aluminum induced osteomalacia. The dialysis patient is exposed to aluminum in the dialysate water as well as from medications (Table 12). The problem of water contamination is no longer an issue with the improved methods of water purification now in use. Most exposure now comes from aluminum containing

Table 12
Aluminum Induced Osteomalacia

1. Water no longer contaminated
2. Al antacids the primary source now
3. Secondary hyperparathyroidism protects
4. Bone and joint pains due to Al deposition
5. Low bone turnover rate predisposes diabetics

antacids. However, aluminum bone disease and encephalopathy are becoming less common with the move away from aluminum containing phosphate binders and the substitution of calcium binders for this purpose. Nevertheless, some patients with refractory hyperphosphatemia still require aluminum binders. Secondary hyperparathyroidism seems to protect against aluminum induced bone disease, presumably because aluminum deposition at the mineralization front is prevented by the rapid bone turnover (35). Conversely, there appears to be an increased risk of developing symptomatic aluminum-related bone disease in the post parathyroidectomy period when secondary hyperparathyroidism is corrected or following "medical parathyroidectomy" when calcitriol is used to reverse the hyperparathyroid states (36).

Patients with aluminum excess complain of generalized bone and joint pain. Aluminum is deposited in joint spaces in increased amounts in patient who ingest aluminum containing antacids (37). Aluminum concentrations in the synovial fluid may be 2-10 times higher in these patients compared to those not using aluminum binders.

Aluminum bone disease in diabetes. Aluminum bone disease is enhanced in dialysis patients with diabetes and seems to result from a lower than normal bone formation rate. (38,39). Insulin dependent diabetes in patients with normal renal function is associated with a low rate of bone formation and osteopenia (38,40). Andress et al (38) showed that insulin-dependent diabetics with chronic renal failure accumulate aluminum faster than matched controls without diabetes. It is likely that it is the low rate of bone formation rather than some other aspect of diabetes that leads to the increased aluminum accumulation, since the low bone formation that occurs in post parathyroidectomy patients is also associated with enhanced aluminum accumulation (34). The cause of the low bone formation in diabetes is unknown but may be related to a decreased levels of parathyroid hormone (39,41).

Bone biopsy is an important test in the management of patients with renal osteodystrophy. It is mandatory in the surgical management of secondary hyperparathyroidism, since a serious complication of total or subtotal parathyroidectomy is the development of aluminum related osteomalacia (36). High PTH values and the attendant high bone turnover seem to have a protective effect against the development of aluminum induced bone disease (35). Whether parathyroidectomized patients have a propensity to develop aluminum related bone disease because of the deposition of aluminum in the bone prior to the surgery or because of enhanced uptake in the postoperative period, or both, is uncertain. A bone biopsy is the most important and specific method of determining the type and severity of bone disease in the patient with ESRD. One of the key measurements to be made is the bone formation rate which is determined using the technique of double tetracycline labeling. Doses of tetracycline are given 15-20 days

apart and then the biopsy is taken from the iliac crest. The rate of new bone formation per day can then be determined using fluorescence microscopy. In addition, bone sections should be stained for aluminum, as well as iron, for their possible role in causing renal osteodystrophy.

Dialysis Encephalopathy. Dialysis encephalopathy is a neurologic syndrome developing in long-term dialysis patients characterized by myoclonus, mental changes, speech disturbances, hallucinations, and seizures. Increased aluminum is present in the brain tissue of affected patients (42). Original reports concerned geographic clustering of cases which were traced to aluminum contaminated water, while sporadic cases are now more common and more likely due to orally ingested aluminum binders given for phosphate control.

Deferrioxamine (DFO). Removal of excess aluminum using DFO reverses osteomalacia (43,44), aluminum induced anemia (45), and encephalopathy (46). However, it is difficult to determine which patients have the disorder and will benefit from aluminum removal. Unstimulated serum aluminum levels are randomly distributed and do not correlate with time on dialysis (47). The ability of an acute infusion of DFO to stimulate a rise in serum aluminum levels has been used to identify patients with potentially toxic body burdens of aluminum. McCarthy et al (48) evaluated the sensitivity and specificity of the DFO stimulation test in 50 consecutive dialysis patient undergoing bone biopsy. Twenty of the patients had negative bone aluminum and were distinguishable from the patients with a positive bone aluminum stain by a smaller increased in stimulated aluminum and a higher baseline serum iPTH (Table 13).

Table 13
Serum Aluminum and PTH
With DFO Stimulation Test

		Serum Al			
Bone Al	(n)	pre DFO	post DFO	Change	PTH
		(μg/L)			(μleq/L)
Positive	30	120±72	493±293	373±250	336±442
Negative	20	106±78	337±218	231±179	1278±1400

Ref. (48) McCarthy QJM Mar 1990

The baseline serum aluminum did not distinguish the negative from the positive patients. The laboratory sensitivity of stimulated changes in serum aluminum and in iPTH values were also evaluated (Table 14). The most sensitive test for aluminum bone disease was

Table 14

Laboratory Measures of Aluminum Bone Disease

	Sensitivity	Specificity	Predictive Value (%)
Pre-DFO Al >100 ng/ml	57	50	63
Pre-DFO Al >200 ng/ml	17	90	71
Al stim. >200 ng/ml	73	50	69
Al change >300 ng/ml	50	60	68
PTH <200 uleq/ml	50	80	79
Al change >200 ng/ml and PTH <200 µleq/ml	37	90	85

Ref (48) McCarthy QJM Mar 1990

a stimulated change in Al of 200 ng/ml, while the most specific was a pre-DFO Al of greater than 200 ng/ml or a stimulated change of greater than 200 ng/ml and a PTH value less than 200 µleq/ml. Long-term DFO therapy reduced bone aluminum staining in all patients and improved bone histology in most such that the patients with osteomalacia tended to move to a pattern of a mixed lesion or osteitis fibrosa. Only one of three parathyroidectomized patients with the low turnover bone lesion showed improved histology on the post-DFO bone biopsy. The study by McCarthy et al (48) used a dialyzer membrane which had less than half the capacity of the dialyzer used in Case 3 to remove the DFO mobilized aluminum. Using a high flux dialyzer, near complete removal of chelated aluminum now appears to be possible during a single dialysis session (49). Felsenfeld, et al (44) studied the effect of treatment for one year with DFO on bone histology and parathyroid function in 18 patients with aluminum-associated bone disease. They found a decrease in stainable trabecular bone aluminum, and an increase in osteoblastic osteoid, osteoclasts, and bone formation rate. These latter indices also improved in patients who previously had had parathyroidectomy. However, improvements in clinical symptomatology were described as only "moderate." Also, aluminum containing antacids were continued as the primary phosphate binder and may have reduced the overall benefit of the DFO therapy. These studies may have to be reexamined in light of newer and more efficient techniques to remove the DFO-aluminum complexes currently available. Molitoris et al (49) showed that the high flux polysulfone dialyzer membrane had a 4 fold greater clearance of the DFO-aluminum complex compared to the standard cuprophane membrane (Table 15). This technique will not only reduce the time DFO is required, but reduce the intradialytic

Table 15
Dialyzer Clearance of DFO-Al

	Cl_{Al} (ml/min)	t 1/2 (min)
Cuprophane	20±3	538±113
Polysulfone	80±8	112±12

Molitoris Kid Int 34:98, 1988

exposure time to the potentially toxic effects of free DFO, the DFO-aluminum complex, and DFO-iron complexes described below. The use of DFO to remove aluminum carries with it an increased risk of mucormycosis. Boelaert, Fenves, and Coburn (50) have gathered data on 59 patients in an international registry on mucormycosis in dialysis patients (Table 16). 44% of cases were in a

Table 16

DFO and Mucormycosis

1. 59 patients in international registry
   - 44% disseminated mucormycosis
   - 31% rhinocerebral
   - 86% fatal outcome
   - 78% receiving DFO
2. Feroxamine is a siderophore for Rhizopus

Boelaert Am J Kid Dis 1991

disseminated form at presentation; 31% were rhinocerebral at presentation. 86% of cases were fatal. In only 30% of the patients was there a known risk factor for this opportunistic fungal infection (e.g. diabetes, leukemia, immunosuppressive drugs), but 78% of these patients were receiving DFO at the time of diagnosis. While most of the patients received a large weekly dose, 3.3 grams/wk, 20% of the infected patients were receiving 1.5 grams/wk or less. The presumed reason for the increased incidence of this fungal infection is that the deferoxamine-iron chelate, feroxamine, is a siderophore for the species Rhizopus microsporus (51). Also, in the presence of renal failure, feroxamine levels in the serum are sustained. This observation has lead to the practice of giving DFO only once per week, and as in Case 3, intramuscular the evening before dialysis so that sustained feroxamine levels are present in the serum for the shortest possible time before they are removed by dialysis (49). Since hemofiltration using highly permeable dialysis membranes or charcoal hemoperfusion doubles the removal rate of the deferoxamine-aluminum chelate compared with standard hemodialysis membranes (49,52), it is very likely that the same will hold for the removal of feroxamine which is even more efficiently removed by standard cuprophane membrane than the aluminum DFO chelate (53). Chronic DFO therapy, in addition to the

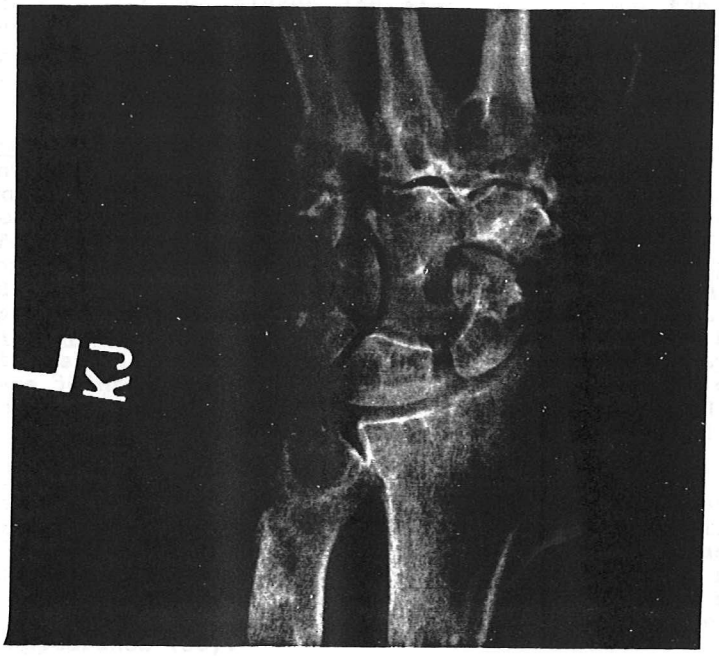
risk of opportunistic infections, also may cause ocular and auditory toxicity (54). Acute administration of DFO has other potentially serious side effects including gastrointestinal disturbances, hypotension, anaphylaxis, and worsening of existing neurological symptoms (55,56). The latter may result from transiently increased CSF levels of aluminum due to passage of the DFO-Aluminum complex (molecular weight, 600 d) across the blood brain barrier (56).

Clinical Points-Case #3. 1. Parathyroidectomy transformed osteitis fibrosa into aluminum related osteomalacia. 2. DFO stimulation indicated excess Al on two occasions and the second stimulation probably produced sustained elevation of Al and, in combination with reduced dialysis time, the encephalopathy. 3. DFO chelation reversed the encephalopathy and bone pain. 5. DFO caused eye and ear side effects. 6. Bone biopsy was an important diagnostic test.

Case 4. (Figure 4)

C.D. is a 74 year old black male with ESRD secondary to adult polycystic kidney disease. He has received hemodialysis since 1972 except for a short period of peritoneal dialysis in 1985. In the past three years his chronic joints complaints have increased. Bone films for many years have shown evidence of hyperparathyroidism ("rugger jersey spine" and "multiple brown tumors"). In mid 1990 he developed right elbow swelling and tenderness and difficulty with standing for prolonged periods. In Feb 1991 his chronic left knee pain of 15 years became acutely worse over a five day period. Examination revealed slight warmth and swelling of the left knee that yielded a bloody fluid on aspiration. X-rays revealed severe osteopenia with cysts in the patella and tibia and findings consistent with a mild compression fracture of the medial tibial plateau. Non-weight bearing and physical therapy returned the patient to his baseline condition within 3 months. In June 1991, he developed acute pain in the left wrist. Physical exam showed that the proximal wrist was very tender but not swollen or warm. X-rays showed no fractures, but multiple cystic lucencies were noted in the carpals, metacarpals, and the distal arm bones without evidence of joint space loss or inflammation (Figure 4). Analgesics and a wrist splint lead to resolution of the pain over the next 6 weeks. When questioned, the patient admitted to chronic pain and stiffness of the hands for several years with loss of motor and sensory function in both hands. Physical findings were consistent with bilateral carpal tunnel syndrome. A current bone survey shows cystic and lytic lesions of all long bones, the hands and wrist, and the cervical spine.

Figure 4



Hemodialysis-related amyloidosis (HRA). Approximately 8 years ago descriptions began to appear of a syndrome in long-term dialysis patient characterized by the presence of carpal tunnel syndrome, bone cysts, pathologic fractures, and swollen painful joints, especially scapulohumeral periarthritis in conjunction with a unique variety of tissue amyloid deposition (57-59) (Table 17). The disorder is closely related to the duration of hemodialysis with a prevalence of 50% in patients who have received more than 12 years of dialysis (60). The tissues in

Table 17

Clinical Features of Hemodialysis-related Amyloidosis

1. Carpal tunnel syndrome
2. Bone cysts
3. Pathologic fractures
4. Scapulohumeral periarthritis
5. Flexor tenosynovitis

dialysis patients most likely to be infiltrated with amyloid are the bones, joints, and synovium (61). However, amyloid may be found in subcutaneous tissue and skin, but unlike the amyloid syndromes unrelated to dialysis (AL, SAA, etc.), HRA is far less commonly found in rectal mucosa, liver, spleen, and blood vessels. However, report of amyloid deposition in non-bone and non-joint tissues suggest that this disorder must be considered a systemic disease (62-64).

Carpal tunnel syndrome. This is the most frequent presenting complaint and its particular predilection for hemodialysis patients was recognized as early as 1975 (65). The incidence in large groups of hemodialysis patients ranges from 2-31% and rarely is seen before 4-5 years of hemodialysis. The average time to onset is approximately 8 years (66). The prevalence is 30% for patients dialyzed for more than nine years (67). Surgical decompression of the carpal tunnel provides the best therapy for these patients.

Scapulohumeral periarthritis. In patients dialyzed for many years, the shoulder is the joint most likely to cause symptoms. When these joints have been surgically explored, amyloid deposits are found in synovial tissue and in the subacromial bursa. Surgical material or joint fluid will usually stain positively for β_2-microglobulin (68).

Patient who have been dialyzed for longer than 8 years frequently develop an effusive arthropathy, often in association with carpal tunnel syndrome. The effusion is often bilateral, especially in the knees and shoulders, and the fluid when aspirated is serous and generally low in cells. Occasionally the fluid is bloody. If these effusions are caused by amyloidosis, the sediment can be centrifuged and stained with Congo red revealing the typical amyloid appearance (58).

Hurst et al (69) surveyed 95 patient receiving chronic hemodialysis for rheumatic diseases and found that most patients could be categorized into 3 relatively distinct classes (Table 18). They noted that the risk of developing HRS was related to age. Also, deposition of amyloid in subchondral bone, but not the synovium caused joint destruction.

Table 18
Arthropathy in Hemodialysis

1. Amyloid-related syndromes
   -tenosynovitis
   -Carpal tunnel syndrome
   -bone cysts
2. Erosive azotemic osteoarthropathy
3. Degenerative joint disease
   -small, large, axial joints

Ref. (69)

The bone lesions of HRA are typically cystic lesions at the ends of long bones. They may be mistakenly called "brown tumors,"

since hyperparathyroid bone disease is very frequent in dialysis patients. The most important risk factor for this disorder is duration on dialysis. The cystic lesions contain amyloid, enlarge with time, may be associated with pathologic fractures, and tend to occur in characteristic locations (Table 19).

Table 19

HRA Bone Cysts

Carpal bones
Fingers
Femoral and humeral heads
Acetabulum
Tibial plateau
Distal radius

The amyloid found in the bone cysts and synovial tissue is similar to other forms of amyloid in its staining properties with Congo red and in exhibiting apple-green birefringence under polarized light. Chemical studies confirm that the material is identical to β_2-microglobulin (70,71). Synovial tissues may also be invaded by AL-type, but this does not seem to be the case for AA-type amyloid (72).

The diagnosis of HRA is dependent on the typical clinical features supported by tissue deposition of amyloid or the characteristic x-ray picture of multiple bone cysts which enlarge over time (Table 20).

Table 20

Diagnosis of HRA

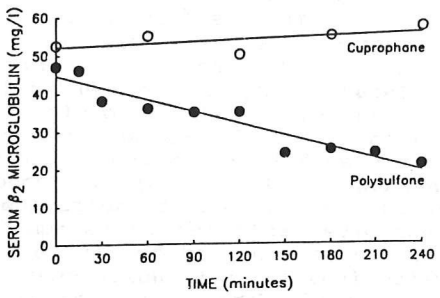
1. Clinical features
2. Radiographic findings
3. Tissue amyloid
4. Serum β_2-microglobulin

Patients dialyzing on a conventional dialyzer will have a serum value between 30-50 mg/L, a range much higher than the normal range of 0.8-3.0 mg/L (73).

Elevated β_2-microglobulin levels are required, but alone they are not sufficient to cause HRA. β_2-microglobulin has a molecular weight of 11,800 d. β_2-microglobulin is normally filtered at the glomerulus and reabsorb and metabolized by proximal tubular cells. In dialysis patients, this mechanism is severely impaired and all patients on hemodialysis have elevated β_2-microglobulin levels. However, HRA does not usually appear until patients have been on dialysis for eight years, and not all patients develop the disease. Patients dialyzed with standard cellulosic membranes have a somewhat higher plasma β_2-microglobulin level than patients

dialyzed with a more porous membrane (74). Also, the presence of even modest residual renal function is associated with enhanced β_2-microglobulin clearance. The highly permeable membranes not only have a higher clearance for β_2-microglobulin, probably because of their intrinsically higher convective transport (75), but β_2-microglobulin also binds directly to these membranes (76). Figure 5 demonstrates the different clearance characteristics for β_2-microglobulin using a conventional cuprophane dialyzer and a high flux polysulfone dialyzer (77). Peritoneal dialysis is not an efficient mode to remove β_2-microglobulin (78). The daily production rate of β_2-microglobulin has been calculated at 3 mg/kg (79). Hemodialysis three times weekly, even with the most efficient of the highly permeable dialyzers, is insufficient to keep up with this production rate (78).

Figure 5



The relationship between β_2-microglobulin levels, HRA, and the dialyzer membrane currently is under study. Both amyloid like bone lesions and carpal tunnel syndrome appear to be less prevalent in patients treated with highly permeable dialysis membranes (80). A multicenter study of HRA demonstrated that patients treated solely with a highly permeable dialyzer membrane displayed bone amyloidosis less frequently than patient treated with cellulosic membranes (81) (Table 21). While it has been suggested that

Table 21

HRA with AN69 or Cellulosic Membrane

	AN69	Cellulosic
Number of patients	115	106
Age	50±12	45±13
Bone amyloidosis	3	17
Carpal tunnel surgery	6	12
CTS and bone amyloid	8	19
Parathyroidectomy	20	26

van Ypersele de Strihou Kid Int 39:1012, 1991

cellulose membranes stimulate the production of β_2-microglobulin, it is more likely that the rise is due merely to ultrafiltration

and hemoconcentration occurring during the dialysis treatment (82). There is a growing appreciation that HRA is a systemic disease (73,83). In a study of 26 patients with histologically confirmed HRA, a high percentage had amyloid positive subcutaneous fat pad aspirations (9/25, 36%), rectal submucosa biopsies (3/7, 43%), and 2-D echocardiograms (12/23, 52%) (83). Skin biopsy, in contrast was negative in all 16 specimens examined. While it is clear that elevated β_2-microglobulin levels in hemodialysis patients are due primarily to reduced renal clearance, the possibility that the dialysis procedure itself may stimulate intradialytic β_2-microglobulin production also has been studied. Hemodialysis patients have enhanced production of β_2-microglobulin by peripheral blood monocytes grown in culture after dialysis with a cuprophan membrane, but not following dialysis with a non-complement activating, polymethylmethacrylate membrane (84). Another mechanism under consideration for the intradialytic generation of β_2-microglobulin is the possible role of endotoxin fragments which transfer to the patient from dialysate contaminated with endotoxin. β_2-microglobulin could be synthesized and released from endotoxin stimulated leukocytes and monocytes (85). How important a component such intradialytic generation of β_2-microglobulin is in the pathogenesis of HRA when compared to the clear evidence for underexcretion is uncertain. The role of bioincompatible versus biocompatible membranes in the generation of β_2-microglobulin is unclear. Bioincompatible membranes are characterized by their propensity to cause an acute decrease in polymorphonuclear leukocytes and activate the complement system. β_2-microglobulin in this schema might be stimulated via circulating cytokines. Although retrospective studies appear to show that bioincompatible membranes are associated with more HRA disease, it is not yet possible to isolate the effect of biocompatibility from that of decreased clearance of β_2-microglobulin.

The therapy of HRA comprises symptomatic and preventive measures (Table 22). Analgesics help with periarticular and bone

Table 22

Therapy of HRA

1. Analgesics
2. Carpal tunnel release
3. Endoscopic joint surgery
4. Prosthetic joint replacement
5. Hemofiltration vs hemodialysis
6. Renal transplantation

pain. The potentially most debilitating aspects of HRA are the carpal tunnel syndrome and the propensity to pathologic fractures from bone cysts in strategic locations (e.g. femoral neck). Since HRA is a progressive disease, early surgical correction of carpal tunnel syndrome seems warranted. Endoscopic surgery on the shoulder with removal of synovium infiltrated by amyloid may give

dramatic relief from pain (86). Replacement of diseased joints with a prosthesis must be determined on an individual basis, but when performed may effectively relieve pain and restore lost mobility. A recommendation to exclusively hemofilter using highly permeable dialysis membranes to prevent and/or treat HRA cannot be endorsed at present. The technology is not universally available, it is clearly more expensive, and prospective studies are not available to justify such a change. Renal transplantation reduces β_2-microglobulin levels to normal and joint pains usually resolve quickly, but, interestingly, β_2-microglobulin radiographic lesion do not heal, even several years post transplantation (87,88).

Clinical points in Case 4. 1. Carpal tunnel syndrome and bone cysts make diagnosis secure. 2. Brown tumors are unusually near joints and multiple tumors are very unusual.

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