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METABOLIC BONE DISEASE

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The rheumatologist has an excellent opportunity to detect and diagnose patients with a variety of metabolic bone diseases. When bone near the articulating surface is involved in metabolic bone disease, it is understandable that the patient will present with findings which on many occasions will simulate a variety of rheumatic afflictions. The following are some examples of patients with medical bone disease who presented initially with features that suggested some form of arthritis. The thoughts expressed are those that have had special interest for the author and are not meant as a detailed review of the large field of medical bone disease.

HYPERPARATHYROIDISM

The first patient is a teen age girl who presented with pain, tenderness and swelling in the region of the knees and, on examination, had marked genu valgum. The bone adjacent to the knees on roentgenograms suggested the possibility of osteitis fibrosa cystica and subsequently the diagnosis of hyperparathyroidism was established. Following removal of a parathyroid adenoma, there was a marked improvement in the symptoms and knee deformities.

Bywaters1 has recently reviewed 19 patients with hyperparathyroidism who initially presented with joint symptoms suggesting some form of arthritis. In 12 of these patients, there was joint pain and tenderness, 8 had actual joint effusions, 11 had soft tissue calcification and/or calcification of the articulating cartilage, and in 14 patients erosions were present in the bone adjacent to the joint spaces.

Hyperparathyroidism should be considered when one is dealing with patients who have rheumatoid-like or other forms of arthritis with atypical features. Involvement of the bone near the articulating hyaline cartilage by osteitis fibrosa cystica will result in destruction of the hyaline cartilage and replacement with fibrous cartilage. As a result of this pathologic process, instability of the joint occurs with secondary degenerative changes, joint effusions and actual thickening of the synovium that may simulate rheumatoid arthritis.

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Hyperparathyroidism may also present as chondrocalcinosis or pseudo-gout characterized by recurrent episodes of joint pain, swelling and effusion interspersed with pain-free intervals. Roentgenograms of the involved joints may show calcification of the articulating cartilage and examination of the joint fluid may show the characteristic pyrophosphate crystals. Chondrocalcinosis should not be a final diagnosis, but should be looked upon as a possible clue to underlying metabolic bone disease; not only hyperparathyroidism, but also other conditions associated with hypercalcemia such as hypervitaminosis D, milk-alkali-syndrome and chronic renal failure with metastatic calcification.

There has been recent interest in the possible relationship between hyperparathyroidism, hyperuricemia and gout. Mintz and associates reported hyperuricemia in 4 of 8 patients with hyperparathyroidism. Gout or a family history of gout was noted in 2 patients of the hyperuricemic group. Since some degree of renal insufficiency is frequently present in hyperparathyroidism, this should always be ruled out first as a possible cause of associated hyperuricemia. In the patients described by Mintz, there was no change in the elevated serum uric acid after surgical correction of the hyperparathyroidism. In addition, the administration of parathyroid hormone did not alter either serum uric acid or uric acid clearances, suggesting that parathyroid hormone alone does not affect uric acid metabolism. It is possible that minor degrees of nephrocalcinosis occurring in hyperparathyroidism might result in a renal tubular defect and interfere with the secretory phase of urinary excretion of uric acid, but this is only speculation. Attempts at case detection for hyperparathyroidism in patients with gout have been carried out but not very rewarding. Further study of this problem is needed before a definite relationship between the two diseases can be confirmed.

There is increasing evidence that parathyroid hormone affects soft tissue as well as the skeleton. A patient was recently reported with spontaneous avulsion of several tendons about the knees. In this patient there was pain, swelling and tenderness about the knees, and initially the patient was thought to have rheumatoid arthritis. Subsequently a diagnosis of hyperparathyroidism was established. Parathyroid hormone appears to have a depolymerizing effect on nonskeletal as well as skeletal collagen. This may explain the hypotonicity, joint laxness and such rare findings as tendon avulsions in hyperparathyroidism. The soft tissue effects of hyperparathyroidism will in the future undoubtedly receive increased attention.

Hyponorathyroidism

Patients with postoperative and idiopathic hypoparathyroidism ordinarily do not present with skeletal symptoms; however, this is not true for pseudohypoparathyroidism. Besides the well-known physical features of patients with pseudohypoparathyroidism, there may be evidence of bone demineralization and subperiosteal resorption. This suggests a parathyroid effect despite the presence of hypocalcemia. Features of osteitis fibrosa in these patients have been described by Kolb and Steinbach and have been given the unwieldy, but meaningful, term pseudohypohyperparathyroidism. Several
of these patients have presented with slipped femoral epiphyses, perhaps the result of weakened bone due to the underlying osteitis fibrosa. It is theorized that the refractoriness to parathyroid hormone at the renal tubular level results in secondary hyperparathyroidism. Under these circumstances and, if the skeleton is sensitive to the effects of the patient's parathyroid hormone, osteitis fibrosa cystica would be the end result. Why these patients persist in having hypocalcemia with parathyroid responsiveness at the skeletal level is not clear. Perhaps the continuing hyperphosphatemia that is a reflection of the renal tubular refractoriness may in some way be responsible. Not all these patients have skeletal responsiveness either to their own or to exogenous parathyroid hormone. Dent in an attempt to explain this enigma has postulated the presence of two parathyroid hormones, one a calcium- and phosphorus-liberating hormone and another whose excess production would manifest itself as osteitis fibrosa and a rise in plasma alkaline phosphatase. He theorizes that it may be possible to have parathyroid hormone effects on the skeleton, giving rise to osteitis fibrosa without liberating calcium from the skeleton. This is contrary to current views which indicate that all major effects of parathyroid hormone are contained in the same molecular structure.

**RENAL OSTEODYSTROPHY**

The next patient is a 7 year old girl who complained of severe pain, swelling and tenderness about the knees which prevented her from walking. On examination she was found to be anemic, severely azotemic and acidotic. Her uremia was due to congenital strictures of the ureters with secondary pyelonephritis. Roentgenograms of her knees demonstrated findings of rickets with widening and irregularity of the epiphyseal lines. Serum calcium was 6 mgm. per cent, phosphorus 8 mgm. per cent and alkaline phosphatase 15 Bodansky units.

Renal osteodystrophy is one of the most complicated of the metabolic bone diseases. There may be evidence not only of rickets or osteomalacia, but also osteitis fibrosa cystica, osteoporosis and even osteosclerosis. All these different pathologic processes may occur near each other in the same bone or in adjacent bones. The theory that the skeletal changes in this condition are secondary to the underlying renal acidosis is not held tenable at the present time. Stanbury, who studied this problem, could not correlate skeletal changes with degree of renal acidosis.

Two approaches to therapy have received recent study. If the main skeletal process in renal osteodystrophy is rickets or osteomalacia, large doses of vitamin D may give symptomatic improvement. This is the case in the patient illustrated. This child had complete disappearance of skeletal pain and tenderness on 50,000 U. vitamin D daily without deterioration of her renal function. With such large doses of vitamin D, these patients should be followed closely since nephrocalcinosis and progression of renal failure is always a possibility. The rickets and osteomalacia in this condition appear to be due to a resistance to the effects of vitamin D at the intestinal level interfering with absorption of calcium. This resistance can be overcome by large doses of vitamin D.
In some patients with renal osteodystrophy, the main skeletal defect is osteitis fibrosa cystica due to secondary hyperparathyroidism as the result of the chronic uremia. Under these circumstances, serum calcium level may be higher than one would ordinarily expect for the degree of renal failure. In several instances, subtotal parathyroidectomy has been carried out with alleviation of the skeletal discomfort from the osteitis fibrosa.

It is becoming increasingly clear that some patients with secondary hyperparathyroidism due to chronic renal disease may have an autonomous parathyroid adenoma superimposed upon secondary hyperparathyroidism. This condition has been called by some tertiary hyperparathyroidism. In these cases, the serum calcium which earlier in the course of the renal failure is depressed, may actually rise to significant hypercalcemic levels with progression of the uremia. It is also possible that autonomous primary hyperplasia may be superimposed upon the secondary hyperparathyroidism of renal failure. The recent article by Golden and associates emphasizes some problems of parathyroid hyperplasia and adenoma in chronic renal disease.

**Vitamin D Resistant Rickets**

The next patient is a 10 year old girl who presented with instability of the right knee joint and genu valgum. Roentgenogram of this joint was compatible with rickets. The serum calcium was normal, the serum inorganic phosphorus was 2 mgm per cent and the alkaline phosphatase 14 Bodansky units. There was no steatorrhea and no systemic acidosis. The diagnosis was late-onset, sporadic vitamin D resistant rickets. There was no family history of a skeletal disorder. The patient had an osteotomy with correction of her deformity and is now asymptomatic on 50,000 U. vitamin D daily plus an oral phosphate solution to tolerance.

The pathogenesis of vitamin D resistant rickets and also its therapy has received increasing attention. There are two main theories as to causation: 1) A congenital defect for absorption of calcium with early hypocalcemia and secondary hyperparathyroidism leading to increased renal clearance of phosphorus. 2) A primary renal tubular defect for phosphorus, secondary hypophosphatemia and the development of rickets or osteomalacia. These two theories are difficult to resolve, and they may not be mutually exclusive. There is evidence, at least in some patients, that oral phosphate supplements to tolerance may result in x-ray evidence of healing of the osteomalacia with improved calcium balance. This suggests that the apparent intestinal defect for absorption of calcium can be corrected if the serum phosphorus is kept at normal levels so that both phosphorus and calcium enter into bone. With improved skeletal deposition of calcium, there may be secondarily improved intestinal absorption of calcium. Personal experience indicates that adults with vitamin D resistant osteomalacia do better with oral phosphate supplements than do children with the disease. It is possible that the lower normal serum phosphorus in adults may have a bearing on this; perhaps the adult skeleton can mineralize at lower levels of serum phosphorus than that which is applicable in children. The higher phosphorus levels necessary in children may be more difficult to attain with oral phosphorus because of the dose-
limiting factor of diarrhea. With the use of phosphorus supplements, less than toxic
doses of vitamin D may have greater effectiveness in treatment of resistant rickets
and osteomalacia.

**OSTEOMALACIA SECONDARY TO URETEROSIGMOIDOSTOMY**

The next patient has been most rewarding from the diagnostic and therapeutic
point of view. The patient is a 55 year old man who presented to the Clinic with
severe pain about the left hip which caused him to limp. The urinary bladder was
removed 10 years previously because of cancer. A colostomy and ureterosigmoido-
dostomy were performed. The CO₂ combining power was 14, serum chloride 114 mEq,
and arterial pH was 7.18. The evidence was in keeping with systemic acidosis
secondary to the uterosigmoidostomy. The serum calcium, phosphorus and phosphatase
surprisingly were normal on two occasions. X-ray of the left hip initially was in-
terpreted as normal. However, laminograms of the left hip showed a typical pseudo-
fracture of the neck of the femur. After bone labeling with tetracycline, a bone
biopsy was performed and examined histologically by Dr. H. Frost. Flagrant osteo-
malacia was present. With 12 grams of bicarbonate daily to correct the acidosis
and 50,000 U. vitamin D, there has been marked improvement in the patient's
hip pain.

The presence of such severe osteomalacia with normal serum calcium, phosphorus
and phosphatase is interesting and illustrative of a number of other patients we have
recently seen. Many of these patients were thought originally to have involutional
osteoporosis, but rib biopsy after appropriate tetracycline labeling and tetrachrome
staining demonstrated histologic evidence of osteomalacia, sometimes in conjunction
with osteoporosis. I strongly feel that the rib biopsy has been most helpful in better
defining a variety of metabolic bone diseases and should be part of the diagnostic
workup in patients with demineralizing bone diseases.

**BONE DYNAMICS IN OSTEOMALACIA**

I would next like to review certain pathogenic and diagnostic aspects of osteo-
malacia. The abnormal osteoid seam is the pathologic hallmark of osteomalacia. After
formation by the osteoblasts, approximately 10 days of growth and aging is
needed before the osteoid seam will accept deposition of mineral in the zone of
demarcation. At this point the osteoid seam becomes mineralized to form lamellar
bone.¹⁰

In the past it has often been assumed that healthy adult skeleton does not
contain osteoid seams. This is not true and, in fact, the norm for osteoid seams in
certain bones at different ages for both sexes has now been determined. This can
be used for a reference standard to define whether bone is indeed osteomalacic.¹⁰

It is important to remember that osteoid balance is dynamic. The amount of
osteoid tissue present at any one time in the skeleton is the result of a constant
balance between the rate of osteoid formation and the rate of mineralization of the
osteoid tissue. The following possibilities of osteoid imbalance may occur, any one
of which may lead to osteomalacic bone: 1) normal formation rate with decreased rate of mineralization, 2) decreased formation rate with a greater decrease in rate of mineralization, 3) increased formation rate with normal rate of mineralization, 4) increased formation rate with a lesser increase in mineralization, 5) any positive formation rate in the presence of a zero mineralization rate, and (6) formation rate increased with a decreased mineralization rate.

The diagnosis of osteomalacic bone is best detected by the study of undecalcified bone sections with special tetrachrome stains. The value of this staining technique over routine decalcified H and E sections in demonstrating osteoid seams can easily be illustrated. These new techniques in bone fixation and staining have allowed us to make a diagnosis of osteomalacia in many instances where its presence was unexpected. The radiologic signs of osteomalacia, except for pseudofractures, are nonspecific and values for serum calcium, phosphorus and phosphatase vary considerably and may be misleading with respect to the diagnosis of osteomalacia.

The following is a list of conditions in which rickets and osteomalacia may occur:

1) Vitamin D deficiency
2) Malabsorption syndromes
   a) postgastrectomy
   b) pancreatic disease
   c) small intestinal disease
   d) hepatic (biliary obstruction)
3) Thyroid and parathyroid
   a) Hyperparathyroidism with osteitis fibrosa
      1. treated
      2. healing state
   b) Hyperthyroidism with bone involvement
4) Renal
   a) glomerular insufficiency (renal osteodystrophy)
   b) tubular
      1. Fanconi syndrome
      2. tubular acidosis
5) Etiologies unknown or not clear
   a) Vitamin D resistant rickets and osteomalacia
   b) hypophosphatasia
   c) marble bone disease
   d) neurofibromatosis
   e) Wilson’s disease
   f) Paget’s disease
   g) beryllium, magnesium, strontium and lead administration
   h) osteoporosis (involutional)
   i) fluoride administration
   j) “axial” osteomalacia
   k) postureterosigmoidostomy
Space does not permit a detailed explanation of known facts regarding pathogenesis in these various types of osteomalacia. It is important to remember that osteomalacic bone may be only one of several features of the metabolic bone disease in those conditions listed. Metabolic bone diseases are seldom pure but usually are a mixture of several pathologic processes progressing or regressing at the same time. Osteomalacic bone is the end result of a continuous spectrum of both systemic and local causal factors. As our knowledge advances and vital factors in the mineralization of osteoid tissue are better defined, more examples of osteomalacia will be clarified as to pathogenesis.

**OSTEOPOROSIS**

Recently, renewed attention has been given to the concept that involutional osteoporosis is the result of a negative calcium balance rather than a decline in anabolic hormone secretion. Dietary histories of patients with osteoporosis have been shown to be deficient in calcium, while calcium supplements given to patients with involutional osteoporosis have resulted in an improved calcium and phosphorus balance.

One of the major difficulties in the study of osteoporosis has been the lack of sensitivity in various roentgenologic techniques for determining bone density. There is increasing evidence that osteoporosis of the axial skeleton can be correlated with a decrease in bone cortical diameter of the metacarpals and midshaft of the femur.\(^\text{11}\) This evidence suggests that all areas of the skeleton are affected by osteoporosis and not just the spine. Further studies\(^\text{11}\) have demonstrated that bone density of the spine, as well as metacarpal and femoral cortex, are not related to calcium intake. Three groups of patients, age and sex matched, were grouped according to low, medium and high calcium intake. In these patients, vertebral density and cortical measurements of the metacarpal and midshaft of the femur were similar in both the low and high calcium intake groups. This suggests that many patients with low calcium intake are able to maintain quantities of bone similar to that seen in patients with a high calcium intake. This does not negate the importance of calcium in the pathogenesis of osteoporosis. It is possible that those patients with low calcium intake have adapted with improved intestinal absorption of calcium or with reduced urinary excretion of calcium and, therefore, have been able to maintain calcium balance. On the other hand, those patients who are unable to adapt to a reduced intake in such a manner may be the very patients who develop osteoporosis. This, of course, holds only if other pathogenic factors for osteoporosis remain the same. A longitudinal study over a period of many years measuring calcium intake, intestinal absorption of calcium, and urinary excretion of calcium will be necessary before the importance of these factors can be defined in any individual patient.

Other recent studies may have pertinence to the pathogenesis of osteoporosis.\(^\text{12}\) The serum antirachitic activity was determined in both Puerto Rican and Michigan women. It was found that in all age groups, the Puerto Rican subjects had a higher serum antirachitic activity than those from Michigan, probably related to greater sun exposure. In conjunction with this, it was found that the serum
calcium and phosphorus levels were significantly lower in the Michigan than in the Puerto Rican subjects. It was also found for the Michigan subjects that patients with osteoporosis had less serum antirachitic activity than their age-matched controls. It is possible, but not proved, that this difference in serum antirachitic activity as well as concentrations of calcium and phosphorus may in some way be related to osteoporosis. Perhaps differences in serum levels of vitamin D, calcium and phosphorus may have a conditioning effect on the skeleton which may be a factor in the development of osteoporosis. It also may help explain the fact that Dr. H. Frost has observed in rib biopsies that approximately 20 per cent of patients with so-called involutional osteoporosis show evidence of osteomalacia as well as osteoporosis. This again emphasizes the fact that medical bone diseases are not pure and that more often than not one is dealing with a spectrum of metabolic bone diseases.

As with the balance concept for the osteoid seam in osteomalacia, it is also important to think of a balance between bone formation and bone resorption in osteoporosis. The decrease in bone mass observed in osteoporosis may result from an imbalance between bone formation and bone resorption. This may arise in the following ways: 1) reduction in bone formation while bone resorption remains unchanged, 2) normal bone formation associated with increased bone resorption, 3) decrease in bone formation in addition to increased bone resorption, 4) an increase in bone formation with a greater increase in bone resorption, and 5) reduction in bone formation greater than a decrease in bone resorption. As knowledge increases, it will be possible to determine the important factors of bone imbalance occurring in each of the several types of osteoporosis. Osteoporosis is not a single disease entity but results from a variety of factors affecting bone accretion, bone resorption, or both.

Rate of bone turnover is an important consideration in osteoporosis. It is apparent that bone may be rapidly formed and rapidly resorbed or, on the other hand, slowly formed and slowly resorbed. Despite varying rates of bone turnover, the actual amount of bone present at any one time or bone balance may be unchanged. Rates of bone turnover can be measured by radiokinetic techniques and also by newer histologic methods. Hyperthyroidism is an example of a high turnover osteoporosis. In this instance, both bone formation rate and bone resorption rate are increased, but bone formation rate is increased less than bone resorption; therefore, a high turnover osteoporosis. The bone histology in hyperthyroidism is complicated in that there is not only osteoporosis, but also osteitis fibrosa and osteomalacia. Cushing’s disease, on the other hand, is an example of low turnover osteoporosis. In this instance, both bone formation rate and bone resorption rate are decreased, but there is a greater decrease in bone formation rate and hence a low turnover osteoporosis.

Perhaps one day the various osteoporoises can all be classified as to whether they are low turnover or high turnover. It is also important to remember that the same concept of rate turnover can be applied to the osteoid seam in osteomalacia, depending upon the rapidity of matrix formation and subsequent mineralization. We can, therefore speak of a high turnover or low turnover osteomalacia.
Considerable recent advances have been made in the study of bone dynamics. To better define the causal factors in metabolic bone disease, a multi-disciplined approach is needed for each medical bone disease. The recently improved histologic techniques, radiokinetic studies for bone accretion and bone resorption and total balances for calcium and phosphorus should be performed concomitantly in patients with a variety of medical bone diseases before the various causative factors can be better defined.

REFERENCES