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Ed. Note - This overview was originally presented at the International Symposium on Clinical Disorders of Bone and Mineral Metabolism, May 9-13, 1983. The following list indicates the presentations given in this session at the Symposium and the contents of the corresponding chapter in the Proceedings of the Symposium published by Excerpta Medica. The numbers in parentheses refer to pages in this volume. Complete information about the contents of the Proceedings can be found at the back of this issue.

Spatial distributions of aluminum, phosphorus and calcium in mineralizing epiphyseal growth plates of aluminum-treated rats by electron spectroscopic imaging. A.L. Arsenault, F.P. Ottensmeyer, and A.B. Hodsman (220)

Histologic evolution of vitamin-D depletion in patients with intestinal malabsorption of dietary deficiency. D.S. Rao, A. Villanueva, M. Matthews, B. Pumo, B. Frame, M. Kleerekoper, and A.M. Parfitt (224)

Primary biliary cirrhosis and alcoholic cirrhosis as examples of chronic liver disease associated with bone disease. R.R. Recker, W. Maddrey, H. Herlong, M. Sorrell, and R. Russell (227)

Chronic hypophosphatemia without osteomalacia. M.C. de Vernejoul, P.J. Marie, L. Miravet, and A. Ryckewaert (232)

Bone disease in patients receiving total parenteral nutrition. S.M. Ott, N.A. Maloney, G.L. Klein, A.C. Alfrey, M.E. Ament, J.W. Coburn, and D.J. Sherrard (237)

The pathogenesis of tumor-induced osteomalacia: A new perspective. P.C. Brazy, B. Lobuagh, K.W. Lyles, and M.K. Drezner (242)

Recent advances in laboratory methods and techniques related to bone and mineral metabolism have provided a detailed study of factors important in bone formation. Osteomalacia results from a disturbance in mineralization of bone matrix. Theoretically, bone matrix may fail to mineralize because of abnormalities in collagen and matrix proteins, or because of an alteration in mineral metabolism at the mineralization front. The result is an accumulation of increased quantities of unmineralized bone matrix (osteoid) over bone surfaces.

Rickets is more apparent in children who have otherwise normal growth patterns, including that of the cartilage present in the growth plates of long bones. Likewise, osteomalacia is less apt to occur when normal bone matrix formation is deficient. In order for a defect in bone mineralization to be fully expressed, adequate bone matrix must first be deposited.

The Table lists some of the factors currently considered to be possibly significant in the formation of bone matrix and mineralization.

Recent studies suggest that bone resorption itself may be important as an initiating event for osteoblast formation and function in the bone remodeling unit (BMU). A high molecular weight polypeptide which has been isolated from tissue cultures and demineralized human bone matrix, stimulates osteoblast proliferation and matrix formation. Impaired release or other defect in this coupling or skeletal growth factor could theoretically influence subsequent osteoblast vigor and function.

Collagen synthesis is the initial, major component of bone matrix formation. Maturation of collagen, which appears to be important for mineralization, is characterized by increasing intra- and extrafibrillar cross-linking of collagen fibers. Some defects in mineralization may result from an abnormality in collagen structure. For instance, in the rare skeletal disorder known as fibro-

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genesis imperfecta ossium, marked distortion of the normally polarized collagen fibers appears to result in impaired mineralization and increased numbers of widened osteoid seams.

The chronologic age of the person as well as the age of the osteoblasts may influence the rate and extent of matrix formation. Decreases in the matrix appositional rate correlates with age and distance from the cement line in individual BMUs. Only insulin and growth hormone, the latter via somatomedin, directly stimulate bone collagen synthesis. Other hormones primarily play a modulating role in collagen formation.

Recently, noncollagenous bone matrix proteins have been evaluated as possible causes of defective mineralization. Osteocalcin (gla protein) has been extensively studied, but its ultimate role in bone metabolism is still to be determined. Osteocalcin has an affinity for binding to hydroxyapatite but only after the latter's maturation from an initial amorphous mineral phase. Another bone matrix protein, osteonectin appears to facilitate the nucleation of calcium phosphate mineral onto the surface of type I collagen.

Proteoglycans and glycoproteins are other important extracollagenous proteins in bone matrix. While their role in mineralization needs further clarification, they do have a high binding affinity for calcium, which apparently depends on the presence of a large number of free acidic groups. Theoretically, excessive calcium binding to proteoglycans might interfere with normal mineral deposition at the mineralization front. In fact, certain rare forms of osteomalacia may be related to a defect in concentration or function of one or more of the matrix proteins. One form of osteomalacia that could result from such a defect is axial osteomalacia. In this skeletal affliction, osteomalacia of the axial skeleton (exhibiting a coarsened trabecular pattern on skeletal x-rays) is not associated with any obvious disturbance in mineral or vitamin D metabolism. An abnormality in one of the extracollagenous matrix proteins could account for this mineralization defect.

Because methods of study are available, most identified forms of osteomalacia have been related to disturbances in mineral and vitamin D metabolism. After appropriate maturation of bone matrix over a period of 10 to 15 days, primary mineralization occurs, and about 80% of the mineral is deposited in the first few days. This primary mineralization is largely controlled by the osteoblasts and nearby osteoid osteocytes. The remainder of the mineral is deposited at a slower rate over a six-month period or more, a process known as secondary mineralization. Osteoblast influence is less important in this latter phase of mineral deposition.

A number of precisely timed chemical and physiological factors must interact for mineralization to proceed normally. Ambient concentrations of calcium and particularly of phosphate are important. Since osteomalacia occurs in many patients with chronic hypophosphatemia, other modulating factors are also important. In this section, M.C. de Vernejoul and associates (pp. 232 ff.) report on 19 male patients with chronic hypophosphatemia due to a renal phosphate leak independent of parathyroid hormone. While there was no osteoid accumulation, decreased osteoblast appositional rate was nevertheless present. As in rickets, normal growth of bone matrix may be necessary before a mineralization defect can be fully expressed.

Relatives of patients with X-linked hypophosphatemic rickets and osteomalacia may exhibit hypophosphatemia without apparent bone involvement. However, many of these patients have not had careful bone biopsy studies with current histomorphometric techniques to exclude a defect in mineralization. Chronic hypocalcemia appears to result in rickets and osteomalacia only

TABLE

Factors Influencing Bone Matrix Formation and Mineralization

Bone resorption in bone remodeling units (BRUs)
- Release of a coupling factor that stimulates osteoblasts

Osteoblast function
- Collagen formation and maturation
  1. Chronologic age of person
  2. Insulin
  3. Growth hormone (via somatomedin)
- Bone matrix proteins
  1. Osteocalcin (Gla protein)
  2. Osteonectin
  3. Proteoglycans

Mineralization at the mineralization front
- Ambient Ca, PO_4 concentrations
- pH at mineralization front
- Amorphous Ca, PO_4 (ACP) preceding hydroxyapatite formation (?)
- Vitamin D metabolites
  1. Maintain adequate ambient Ca, PO_4 levels
  2. (?) Direct effect on osteoblasts and/or mineralization front
- Parathyroid hormone
- Piezoelectric fields (exercise and stress)
- Inhibitors of mineralization
  1. Pyrophosphates
  2. ATP (adenosine triphosphate)
  3. Foreign ions, such as aluminum

  } destroyed by phosphatases and ATPases
- Matrix vesicles
  1. Facilitates mineral and enzyme concentration at the mineralization front

rarely. Examples are seen primarily in rapidly growing children who have subsisted on a calcium deficient diet.

Hydrogen ion concentration appears to be an important clinical factor at the mineralization front. Chronic systemic acidosis, as occurs in patients who have undergone ureterosigmoidostomy, can result in osteomalacia, even in the presence of normal serum levels of calcium and phosphorus.

Most theories of calcification suggest that crystalline hydroxyapatite is preceded by an amorphous noncrystalline calcium phosphate complex, although recent studies have questioned the validity of this concept.

The role of several vitamin D metabolites in bone mineralization is discussed extensively elsewhere in this Proceedings. The importance of these metabolites in maintaining adequate serum concentrations of calcium and phosphorus is unquestioned. Whether they have an additional direct effect on osteoblasts or on mineralization is hotly debated.

Parathyroid hormone appears to directly affect or enhance the availability of minerals at the mineralization front. In some patients with renal osteodystrophy decreased parathyroid function appears to increase the tendency toward a form of osteomalacia that resists the usual treatment.

Exercise by initiating shearing forces on mineral crystals induces electrical fields (piezoelectrical) that may influence bone formation. Fracture non-union is now being successfully treated in some instances by application of low-grade pulsed electrical currents. The importance of such electrical fields in the process of normal matrix formation and mineralization may be important but is difficult to prove.

Just as important as the factors that enhance mineralization of bone matrix are the inhibitors of mineralization that have been identified in bone. Both pyrophosphates and ATP are known to impede different phases of mineral formation and deposition, and removing these inhibitors by endogenous pyrophosphatases (phosphatases) and ATPases encourages mineralization. In hypophosphatasia, a condition with a deficiency of alkaline phosphatase and an increase in the inhibitor phosphoethanolamine, mineralization inhibitors may play an important role in the development of rickets and osteomalacia.

Much current investigation is centered on the role of matrix vesicles in mineralization of cartilage and bone matrix. These structures are detected by ultrastructural examination at mineralizing sites in cartilage and bone. They consist of membrane-bound concentrations of minerals and enzymes, appearing at the initial site of mineral deposition.

Bone matrix formation and its mineralization is a complex process, and many possibilities exist for metabolic defects which may lead to impaired mineralization. Further use of electron spectroscopic imaging, as described by Arsenault and associates (pp. 220 ff.) should help define the factors important for mineral deposition. These authors demonstrated that an increased concentration of aluminum at the zone of calcification in the growth plate retards normal mineralization in aluminum-treated rats. Other studies have demonstrated the importance of aluminum in inhibiting mineralization, both in the treatment resistant osteomalacia observed in hemodialysis patients with renal osteodystrophy and in patients who have been maintained on total parenteral nutrition. The use of electron probes in association with histochemical techniques offers promise in the study of the mineralization process. One day we may have a detailed map of the osteoid seam, where the concentrations of all important factors needed for normal mineralization can be measured, and variations from normal can be detected.

Bone histomorphometry with the use of double tetracycline labeling techniques and undecalcified bone sections has come of age. An absence of osteomalacia, or at the other extreme, florid osteomalacia, can readily be identified by most established calcified tissue laboratories. However, there is less agreement on criteria for the earliest histomorphometric signs of osteomalacia, especially when accompanied by secondary hyperparathyroidism. International agreement should be sought in establishing histodynamic criteria for all stages of osteomalacia so that studies from different clinical research centers can be compared more readily. Rao and others (pp. 224 ff.) in Parfitt's laboratory at Henry Ford Hospital addressed this problem. As kinetic criteria in making the diagnosis of osteomalacia, these investigators use a mean osteoid seam width of greater than 15.0 μm and a mineralization lag time of greater than 100 days. They stressed that the early effects of hypovitaminosis D are mainly those of secondary hyperparathyroidism. As vitamin D deficient osteopathy progresses, the mineralization defect becomes more apparent, with a progressive accumulation of osteoid.

Metabolic bone disease is a common problem in patients with chronic liver disease. Patients with chronic biliary tract obstruction are more likely to have osteomalacia and patients with chronic diffuse hepatocellular disease are more likely to have osteoporosis. Important etiologic factors are defective vitamin D and 25 hydroxyvitamin D absorption, impaired synthesis of 25 hydroxyvitamin D, the deleterious effects of chronic alcoholism on the skel-

eton, hypoproteinemia, and other ill-defined nutritional deficiencies. In view of this, the findings of Recker and associates (pp. 227 ff.) in patients with primary biliary and alcoholic cirrhosis were somewhat surprising. They found no evidence of vitamin D deficiency or osteomalacia, and bone histologic changes in both groups of patients were indistinguishable from those patients with postmenopausal osteoporosis.

Much work still needs to be done to determine the pathogenesis of the bone disease in patients with chronic liver disorders. The type, degree, and duration of liver disease needs to be correlated with defects in mineral and vitamin D metabolism as well as with histomorphometric changes in the skeleton. The results of Recker and associates are discouraging with respect to the possibility of effective treatment in patients with metabolic bone disease due to chronic liver failure, no matter what the underlying etiology.

Many believe that sporadic hypophosphatemic osteomalacia in the adult is almost always related to an underlying tumor, usually mesenchymal. Such tumors may be quite small and difficult to detect, but the effort to find them is worthwhile, since successful removal often improves or cures the underlying osteomalacia. Renal phosphate wastage and hypophosphatemia appear to cause osteomalacia in such patients.

Studies reported by Drezner and associates (pp. 242 ff.) shed further light on this paraneoplastic syndrome of tumor-induced osteomalacia. Their studies suggested further evidence of a tumor-induced alteration of vitamin D metabolism which may cause a urinary phosphate leak. The tumor-producing agent that interferes with renal 1-hydroxylation of 25 hydroxyvitamin D has so far eluded identification.

Identifiable causes of osteomalacia continue to increase. Not surprisingly, foreign ions deposited at the mineralization front can interfere with normal mineralization. Ott and associates (pp. 237 ff.) presented evidence that the etiology of the metabolic bone disease observed in patients receiving total parenteral nutrition (TPN) is somewhat similar to the resistant form of osteomalacia observed in some patients with renal osteodystrophy who have been maintained on hemodialysis. In both conditions, aluminum from exogenous sources appears to interfere with normal mineral deposition. Removal of the aluminum after the use of desferrioxamine allows normal matrix mineralization to be restored. In bone disease associated with total parenteral nutrition, aluminum contamination of the casein used in the TPN solution may be the culprit. Steps should be taken to insure that TPN solutions do not contain aluminum or other potentially toxic trace elements that can impair normal mineralization. If this approach is effective, perhaps the painful disabling bone disease seen in these patients will no longer be observed. However, it should be remembered that not all workers have had a similar experience with regard to aluminum as an etiologic agent in TPN bone disease. This bone disorder may have more than one cause.