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Miscellaneous Disorders of Calcium and Bone Metabolism

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Pathophysiology of Hypercalcemia

During this section of the meeting a miscellaneous group of disorders affecting calcium homeostasis and bone metabolism were reviewed by investigators with special experience with these particular disorders. Kanis et al (1) discussed the distribution of calcium in normal plasma, the importance of binding to plasma proteins, and the effects that this has on interpretation of measurements of total plasma calcium. They discussed the transport of calcium between the extracellular fluid and the gut, bone, and the kidney and stressed the importance of the kidney and in particular renal tubular calcium reabsorption in calcium homeostasis. They then reviewed how careful determination of urine calcium excretion may give insight into calcium fluxes from the skeleton and calcium absorption from the gut.

Hypercalcemia: Solid Tumors

One of the commonest causes of hypercalcemia is malignant disease. Kanis et al (1) indicated that hypercalcemia occurs in malignant disease in a number of different settings. Martin (2) discussed a newly described factor associated with one of these settings, namely the humoral hypercalcemia of malignancy. In this syndrome, a solid tumor produces a humoral factor which alone or in concert with other factors stimulates osteoclastic bone resorption, enhances renal tubular calcium reabsorption, and increases urinary cyclic AMP. Martin described a biological activity from one of these tumors which stimulated adenylate cyclase activity in bone cells and in renal membranes, whose effects were blocked by synthetic antagonists to parathyroid hormone (PTH) and which was not affected by antisera to PTH. He described the purification and molecular cloning of this factor and the biological effects of synthetic fragments. This factor, which was referred to as the PTH-related protein, has considerable homology to authentic parathyroid hormone in the N-terminal region since eight of the first 13 amino acids are identical. It binds to the PTH receptor and activates it. It stimulates bone resorption and renal tubular calcium reabsorption and increases plasma calcium in vivo. Immunoreactive PTH-rP was found in a variety of tumors, some of which are associated with hypercalcemia and some of which are not.

Mechanisms of Hypercalcemia in Hematologic Malignancies

Factors which are implicated in the hypercalcemia associated with hematologic malignancies were described (3). In myeloma, hypercalcemia occurs as a consequence of increased bone resorption usually associated with decreased glomerular filtration. In this malignancy, the tumor cells produce a cytokine (lymphotoxin) which stimulates osteoclastic bone resorption in vitro and in vivo and increases plasma calcium in vivo. In some lymphomas associated with hypercalcemia, there is increased production of 1,25-dihydroxyvitamin D. This has been found in association with adult T-cell lymphomas, with B-cell lymphomas, and in occasional cases with Hodgkin disease. It seems likely in these circumstances that the neoplastic lymphoid cells have developed the capacity to synthesize 1,25-dihydroxyvitamin D.

Paget Disease of Bone: Assessment, Therapy, and Secondary Prevention

Bijvoet et al (4) gave an update of Paget disease of bone. This bone disorder is characterized by a primary abnormality in the osteoclast which is accompanied by morphologic abnormalities which include increased multinucleation, increased functional capacity, and the presence of intranuclear inclusion bodies. These intranuclear inclusion bodies seem likely to be due to a slow virus which is probably the primary cause of this disorder. Paget disease which is associated with pain or deformity can be treated with calcitonin or with one of the drugs of the biphosphonate family. Bijvoet et al stressed the utility of the newer biphosphonates, particularly the amino biphosphonates, which are more potent than the first-generation agents, produce fewer side effects, and may lead to better and more prolonged therapeutic responses.

Renal Calculi: Update

Pak (5) discussed the current status of pathophysiology, diagnosis, and medical management of renal calculi. He reviewed the history of the pathophysiologic approach to diagnosis and treatment of recurrent renal calculi. He discussed the three major mechanisms thought responsible for hypercalciuria—

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absorptive hypercalciuria, resorptive hypercalciuria, and renal leak hypercalciuria—and reported on other less common mechanisms including the primary renal phosphate leak group, the group associated with primary enhancement of 1,25 D production, and the group with combined renal tubular disturbances which lead to hypercalciuria. Pak reviewed the role of hypocitruria which is present in 70% to 80% of patients with recurrent renal calculi and hypercalciuria. Hypocitruria has multiple causes, is easily diagnosed, and readily corrected by potassium citrate, an effective drug which reduces stone formation in these patients. In discussing the utility of medical prevention of recurrent renal calculi with the use of thiazides and potassium citrate, he suggested that despite the recent striking advances in the surgical approach to recurrent renal stones, medical therapy had a useful place in prevention of further development of stones, reduction of the need for further surgery, and as a cost-effective form of therapy. However, he stressed that medical therapy does not cure the underlying defect responsible for this disorder which still requires diagnostic evaluation for careful choice of therapy.

Current Problems in Renal Osteodystrophy

Recent concepts of the pathophysiology of renal bone disease were discussed by Boyce et al (6). Renal bone disease is comprised of three main pathologic entities: osteitis fibrosa (secondary hyperparathyroidism), osteomalacia responsive to vitamin D metabolites, and aluminum bone disease. Boyce et al showed that aluminum is an important pathophysiologic agent in bone disease associated with chronic renal disease and is responsible for a syndrome characterized by resistance to therapy with 1,25-dihydroxyvitamin D, a relative decrease in serum immunoreactive parathyroid hormone, a relative decrease in alkaline phosphatase, and the bone biopsy picture of osteomalacia. There are several variants to the bone biopsy picture. These include pure osteomalacia with low mineralization rates, thick osteoid seams and no evidence of osteitis fibrosa, a mixed picture of osteomalacia and osteitis fibrosa, and an aplastic or adynamic biopsy appearance associated with low bone turnover. They pointed out that patients who are particularly at risk for aluminum intoxication were those who were hyperabsorbers of aluminum, those who used dialysis water in which aluminum was not removed by treatment of water with reverse osmosis or deionization, and those who ingest large amounts of aluminum binders. They then reviewed the difficulties in diagnosis of aluminum bone disease without a bone biopsy. This can be made with the desferrioxamine test followed by measurement of the serum aluminum response, although this test is not uniformly reliable. They indicated the potential problems of patients with aluminum bone disease who were subjected to parathyroidectomy and concluded by indicating that hypercalcemia in a patient with chronic renal disease should not be treated by parathyroidectomy unless aluminum bone disease has been carefully excluded, that aluminum toxicity is still an important cause of renal bone disease, and that the role of parathyroidectomy in exacerbating aluminum bone disease in a patient with underlying increased aluminum content in bone remains unclear.

The Pathogenesis and Clinical Course of Multiple Endocrine Neoplasia Type 2A

The session concluded with a review of the multiple endocrine neoplasia type 2A (MEN-2A) syndrome by Gagel (7). This syndrome comprises medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia. It was first described by Sipple in 1961. Gagel showed how this syndrome has gone through three phases beginning with the clinical description in the 1960s, followed by the use of calcitonin measurement in the diagnosis and screening of asymptomatic patients in the 1970s, and then by recent advances in understanding the abnormalities in gene function which lead to the molecular derangements in patients with this syndrome. He pointed out that the thyroid disease almost always occurs first and that the adrenal disease is a particularly difficult problem because it is frequently diffuse and bilateral. However, the adrenal tumors are rarely malignant, are almost always intraadrenal, and usually secrete epinephrine. His preference is that a patient with evidence for disease in only one adrenal should undergo unilateral adrenalectomy initially. Thyroidectomy should be performed on individuals with abnormalities in calcitonin secretion at the earliest feasible time. Recently, the gene responsible for this disorder has been mapped to chromosome 10 at a point near the centromere. It appears most likely that oncogenesis in this disorder is due to a deletion of a regulatory gene similar to that which has been described in patients with retinoblastoma. In MEN-2A, this deletional mutation is present near the centromere of chromosome 10. It is hoped that these studies will lead soon to the ability to diagnose this disease at birth which may lead to changes in the therapeutic approach (particularly with respect to timing of thyroidectomy) and an improvement in the overall prognosis. At the present time, in patients who are screened and diagnosed as having underlying thyroid disease before the onset of symptoms, about 90% are disease-free at five years if they are subjected to total thyroidectomy.

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