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424 Paget’s Disease and Other Dysplasias of Bone

Osteoporosis and related fractures are serious side effects of chronic glucocorticoid therapy. Because the effects of glucocorticoids on the skeleton are often superimposed on the consequences of aging and menopause, it is not surprising that postmenopausal women and older men are most frequently affected. The skeletal response to glucocorti coids is remarkably heterogeneous, however, and even young, growing individuals treated with glucocorticoids can present with fractures. The risk of fractures depends on the dose and duration of gluco corticoid therapy, although recent data suggest that there may be no completely safe dose. Bone loss is more rapid during the early months of treatment, and trabecular bone is affected more severely than corti cal bone. As a result, fractures have been shown to increase within 3 months of glucocorticoid treatment. There is an increase in fracture risk in both the axial skeleton and the appendicular skeleton, including risk of hip fracture. Bone loss can occur with any route of glucocorti coid administration, including high-dose inhaled glucocorticoids and intra-articular injections. Alternate-day delivery does not appear to ameliorate the skeletal effects of glucocorticoids. ■ ■PATHOPHYSIOLOGY Glucocorticoids increase bone loss by multiple mechanisms, includ ing (1) inhibition of osteoblast function and an increase in osteoblast apoptosis, resulting in impaired synthesis of new bone; (2) stimula tion of bone resorption, probably as a secondary effect; (3) impair ment of the absorption of calcium across the intestine, probably by a vitamin D–independent effect; (4) increase of urinary calcium loss and perhaps induction of some degree of secondary hyperparathyroidism; (5) reduction of adrenal androgens and suppression of ovarian and testicular secretion of estrogens and androgens; and (6) induction of glucocorticoid myopathy, which may exacerbate effects on skeletal and calcium homeostasis as well as increase the risk of falls. ■ ■EVALUATION OF THE PATIENT Because of the high prevalence of GCIOP, it is important to evaluate the status of the skeleton in all patients starting or already receiving long-term glucocorticoid therapy. Modifiable risk factors should be identified, including those for falls. Examination should include testing of height and muscle strength. Laboratory evaluation should include an assessment of 24-h urinary calcium. All patients on long-term

(>3 months) glucocorticoids should have measurement of bone mass at both the spine and the hip using DXA. If only one skeletal site can be measured, it is best to assess the spine in individuals <60 years and the hip in those >60 years. ■ ■PREVENTION Bone loss caused by glucocorticoids

can be prevented, and the risk of fractures significantly reduced. Strategies must include using the lowest dose of glucocorticoid for disease management. Topical and inhaled routes of administration are preferred, where appropriate. Risk factor reduction is important, including smoking cessation, limitation of alcohol consumption, and participation in weight-bearing and resis tance exercise, when appropriate. All patients should receive an ade quate calcium and vitamin D intake from the diet or from supplements. TREATMENT Glucocorticoid-Induced Osteoporosis Several bisphosphonates (alendronate, risedronate, and zoledronic acid) have been demonstrated in large clinical trials to reduce the risk of fractures in patients being treated with glucocorticoids and are FDA approved for the treatment of GCIOP. Teriparatide is also approved for treatment of GCIOP. In one trial comparing teripara tide with alendronate, BMD increases were much greater and verte bral fracture risk reduction was greater with teriparatide compared with alendronate. A study of denosumab indicates greater efficacy of denosumab compared with risedronate for treatment of GCIOP. There are no data for romosozumab in GCIOP. The American Col lege of Rheumatology has published guidelines for the management of GCIOP.

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Paget’s Disease and

Other Dysplasias of Bone PAGET’S DISEASE OF BONE Paget’s disease is a localized bone-remodeling disorder that affects widespread, noncontiguous areas of the skeleton. The pathologic pro cess is initiated by overactive osteoclastic bone resorption followed by a compensatory increase in osteoblastic new bone formation, resulting in a structurally disorganized mosaic of woven and lamellar bone. Pagetic bone is expanded, less compact, and more vascular; thus, it is more susceptible to deformities and fractures. Although most patients are asymptomatic,

symptoms resulting directly from bony involvement (bone pain, secondary arthritis, fractures) or secondarily from the expansion of bone causing compression of surrounding neural tissue are not uncommon. Epidemiology There is a marked geographic variation in the frequency of Paget's disease, with high prevalence in Western Europe (Great Britain, France, and Germany, but not Switzerland or Scandinavia) and among those who have immigrated to Australia, New Zealand, South Africa, and North and South America. The disease is rare in native populations of the Americas, Africa, Asia, and the Middle East; when it does occur, the affected subjects usually have evidence of

European ancestry, supporting the migration theory. For unclear rea sons, the prevalence and severity of Paget's disease are decreasing, and the age of diagnosis is increasing.

The prevalence is greater in males and increases with age. Autopsy series reveal Paget's disease in ~3% of those over age 40. Prevalence of positive skeletal radiographs in patients aged >55 years is 2.5% for men and 1.6% for women. Elevated alkaline phosphatase (ALP) levels in asymptomatic patients have an age-adjusted incidence of 12.7 and 7 per 100,000 person-years in men and women, respectively. Etiology The etiology of Paget's disease of bone remains unknown, but evidence supports both genetic and viral etiologies. A positive family history is found in 15–25% of patients and, when present, raises the prevalence of the disease seven- to tenfold among first-degree relatives. PART 12 Endocrinology and Metabolism A clear genetic basis has been established for several rare familial bone disorders that clinically and radiographically resemble Paget's disease but have more severe presentation and earlier onset. A homo zygous deletion of the TNFRSF11B gene, which encodes osteoprotegrin (Fig. 424-1), causes juvenile Paget's disease, also known as familial idiopathic hyperphosphatasia, a disorder characterized by uncontrolled osteoclastic differentiation and resorption. Familial patterns of disease in several large kindred are consistent with an autosomal dominant pattern of inheritance with variable penetrance. Familial expansile osteolysis, expansile skeletal hyperphosphatasia, and early-onset Paget's disease are associated with mutations in the TNFRSF11A gene, which encodes RANK (receptor activator of nuclear factor-κB), a member of the tumor necrosis factor superfamily critical for osteoclast differentia tion (Fig. 424-1). A mutation in profilin 1, a small actin protein that acts as a tumor suppressor, also causes early-onset Paget's disease with a predisposition for the development of osteosarcoma. Finally, muta tions in the gene for valosin-containing protein cause a rare syndrome with autosomal dominant inheritance and variable penetrance known as inclusion body myopathy with Paget's disease and frontotemporal Mesenchymal cell M-CSF c-fms OPG + RANK L Osteoclast precursor IL-1, IL-6 IGF-1 IGF-2 RANK Osteoblasts Osteoblasts Collagen osteocalcin Osteoclast FIGURE 424-1 Diagram illustrating factors that promote differentiation and function of osteoclasts and osteoblasts and the role of the RANK pathway. Stromal bone marrow (mesenchymal) cells and differentiated osteoblasts produce multiple growth factors and cytokines, including macrophage colony-stimulating factor (M-CSF), to modulate osteoclastogenesis. RANKL (receptor activator of nuclear factor-κB [NF-κB] ligand) is produced by osteoblast progenitors and mature osteoblasts and can bind to a soluble decoy receptor known as osteoprotegerin (OPG) to inhibit RANKL action. Alternatively, a cell-cell interaction between osteoblast and osteoclast progenitors allows RANKL to bind to its membranebound receptor, RANK, thereby stimulating osteoclast differentiation and function. RANK binds intracellular proteins called tumor necrosis factor receptor–associated factors (TRAFs) that mediate receptor signaling through transcription factors such as NF-κB. M-CSF binds to its receptor, c-fms, which is the cellular homologue of the fms oncogene. See text for the

potential role of these pathways in disorders of osteoclast function such as Paget’s disease and osteopetrosis. IGF, insulin-like growth factor; IL, interleukin.

dementia (IBMPFD). The role of genetic factors is less clear in the more common form of late-onset Paget’s disease. The most common mutations identified in familial and sporadic cases of Paget’s disease have been in the SQSTM1 gene (sequestasome-1 or p62 protein) in the C-terminal ubiquitin-binding domain. The other candidate genes include CSF1 (1p13), which encodes macrophage colony-stimulating factor (M-CSF), a cytokine that is required for osteoclast differentia tion; RIN3 (14q32), which encodes a guanine exchange factor called Rab and Ras interactor 3; OPTN (10p13), which is involved in regu lating nuclear factor (NF)-κB; TNFRSF11A, mentioned earlier; and TM7SF4, which encodes dendritic cell–specific transmembrane protein (DC-STAMP), a molecule that is essential for fusion of the osteoclast. The phenotypic variability in patients with SQSTM1 mutations sug gests that additional factors, such as other genetic influences or viral infection, may influence clinical expression of the disease. Several lines of evidence suggest that a viral infection may contrib ute to the clinical manifestations of Paget’s disease, including (1) the presence of cytoplasmic and nuclear inclusions resembling paramyxo viruses (measles, respiratory syncytial virus, canine distemper virus) in pagetic osteoclasts and (2) viral mRNA in precursor and mature osteoclasts. The viral etiology is further supported by conversion of osteoclast precursors to pagetic-like osteoclasts by vectors containing the measles virus nucleocapsid or matrix genes. The decline in the incidence of Paget’s disease coincides with the widespread vaccination against measles, also consistent with the potential role of virus in the development of the disease. However, the viral etiology has been ques tioned by the inability to culture a live virus from pagetic bone and by failure to clone the full-length viral genes from material obtained from patients with Paget’s disease. Furthermore, patients with Paget’s disease do not have higher antibody levels against paramyxoviruses or measles as compared to controls, nor do antibody levels correlate with disease severity in those with Paget’s disease. Pathophysiology The principal abnormality in Paget’s disease is the increased number and activity of osteoclasts. Pagetic osteoclasts are large, increased 10- to 100-fold in number, and have a greater number of nuclei (as many as 100 compared to 3–5 nuclei in the normal osteoclast). The overactive osteoclasts may create a sevenfold increase in resorptive surfaces and an erosion rate of 9 μg/d (normal is 1 μg/d). Several causes for the increased number and activity of pagetic osteoclasts have been identified: (1) osteoclastic precursors are hyper sensitive to 1,25(OH)2D3; (2) osteoclasts are hyperresponsive to RANK ligand (RANKL), the osteoclast stimulatory factor that mediates the effects of most osteotropic factors on osteoclast formation; (3) marrow stromal cells from pagetic lesions have increased RANKL expression; (4) osteoclast precursor recruitment is increased by interleukin (IL) 6, which is increased in the blood of patients with active Paget’s disease and is overexpressed in pagetic osteoclasts; (5) expression of the proto oncogene c-fos, which increases osteoclastic activity, is increased; and (6) the antiapoptotic oncogene Bcl-2 in pagetic bone is overexpressed. Numerous osteoblasts are recruited to active resorption sites and pro duce large amounts of new bone matrix. As a result, bone turnover is high, and bone mass is normal or increased, not reduced, unless there is concomitant deficiency of calcium and/or vitamin D. The characteristic feature of Paget’s disease is increased bone resorp tion accompanied by accelerated bone formation. An initial osteolytic phase involves prominent bone resorption and marked hypervascular ization. Radiographically, this manifests as an advancing lytic wedge, or “blade of grass” lesion. The second phase is a period of very active bone formation and resorption that replaces normal lamellar bone with haphazard (woven) bone. Fibrous connective tissue may replace nor mal bone

marrow. In the final sclerotic phase, bone resorption declines progressively and leads to a hard, dense, less vascular pagetic or mosaic bone, which represents the so-called burned-out phase of Paget’s disease. All three phases may be present at the same time at different skeletal sites. Clinical Manifestations Diagnosis is often made in asymptom atic patients because they have elevated ALP levels on routine blood chemistry testing or an abnormality on a skeletal radiograph obtained

for another indication. The skeletal sites most commonly involved are the pelvis, vertebral bodies, skull, femur, and tibia. Familial cases with an early presentation often have numerous active sites of skeletal involvement. The most common presenting symptom is pain, which may result from increased bony vascularity, expanding lytic lesions, fractures, bowing, or other deformities. Bowing of the femur or tibia causes gait abnormalities and abnormal mechanical stresses with secondary osteoarthritis of the hip or knee joints. Long bone bowing also causes extremity pain by stretching the muscles attached to the bone softened by the pagetic process. Back pain results from enlarged pagetic ver tebrae, vertebral compression fractures, spinal stenosis, degenerative changes of the joints, and altered body mechanics with kyphosis and forward tilt of the upper back. Rarely, spinal cord compression may result from bone enlargement or from the vascular steal syndrome. Skull involvement may cause headaches, symmetric or asymmetric enlargement of the parietal or frontal bones (frontal bossing), and increased head size. Cranial expansion may narrow cranial foramens and cause neurologic complications including hearing loss from cochlear nerve damage from temporal bone involvement, cranial nerve palsies, and softening of the base of the skull (platybasia) with the risk of brainstem compression. Pagetic involvement of the facial bones may cause facial deformity; loss of teeth and other dental conditions; and, rarely, airway compression. Fractures are serious complications of Paget’s disease and usually occur in long bones at areas of active or advancing lytic lesions. Com mon fracture sites are the femoral shaft and subtrochanteric regions. Neoplasms arising from pagetic bone are rare (<0.5%). The incidence of sarcoma appears to be decreasing, possibly because of earlier, more effective treatment with potent antiresorptive agents. The majority of tumors are osteosarcomas, which usually present with new pain in a long-standing pagetic lesion. Osteoclast-rich benign giant cell tumors may arise in areas adjacent to pagetic bone, and they respond to glu cocorticoid therapy. Cardiovascular complications may occur in patients with involve ment of large (15–35%) portions of the skeleton and a high degree of disease activity (e.g., ALP four times above normal). The extensive arteriovenous shunting and marked increases in blood flow through the vascular pagetic bone lead to a high-output state and cardiac enlargement. However, high-output heart failure is relatively rare and usually develops in patients with concomitant cardiac pathology. In addition, calcific aortic stenosis and diffuse vascular calcifications have been associated with Paget’s disease. Diagnosis The diagnosis may be suggested on clinical examination by the presence of an enlarged skull with frontal bossing, bowing of an extremity, or short stature with simian posturing. An extremity with an FIGURE 424-2 A 48-year-old woman with Paget’s disease of the skull. Left. Lateral radiograph showing areas of both bone resorption and sclerosis. Right. 99mTc hydroxymethylene diphosphonate (HDP) bone scan with anterior, posterior, and lateral views of the skull showing diffuse isotope uptake by the frontal, parietal, occipital, and petrous bones.

area of warmth and tenderness to palpation may suggest an underlying pagetic lesion. Other findings include bony deformity of the pelvis, skull, spine, and extremities; arthritic involvement of the joints adja cent to lesions; and leg-length discrepancy resulting from deformities of the long

bones.

Paget’s disease is usually diagnosed from radiologic and biochemical abnormalities. Radiographic findings typical of Paget’s disease include enlargement or expansion of an entire bone or area of a long bone, cortical thickening, coarsening of trabecular markings, and typical lytic and sclerotic changes. Skull radiographs (Fig. 424-2) reveal regions of “cotton wool,” or osteoporosis circumscripta, thickening of diploic areas, and enlargement and sclerosis of a portion or all of one or more skull bones. Vertebral cortical thickening of the superior and infe rior end plates creates a “picture frame” vertebra. Diffuse radiodense enlargement of a vertebra is referred to as “ivory vertebra.” Pelvic radiographs may demonstrate disruption or fusion of the sacroiliac joints; porotic and radiodense lesions of the ilium with whorls of coarse trabeculation; thickened and sclerotic iliopectineal line (brim sign); and softening with protrusio acetabuli, with axial migration of the hips and functional flexion contracture. Radiographs of long bones reveal bowing deformity and typical pagetic changes of cortical thickening and expansion and areas of lucency and sclerosis (Fig. 424-3). Radio nuclide 99mTc bone scans are less specific but are more sensitive than standard radiographs for identifying sites of active skeletal lesions. Although computed tomography (CT) and magnetic resonance imag ing (MRI) studies are not necessary in most cases, CT may be useful for the assessment of possible fracture, and MRI is necessary to assess the possibility of sarcoma, giant cell tumor, or metastatic disease in pagetic bone. Definitive diagnosis of malignancy often requires bone biopsy. Paget’s Disease and Other Dysplasias of Bone CHAPTER 424 Biochemical evaluation is useful in the diagnosis and management of Paget’s disease. The marked increase in bone turnover can be moni tored using biochemical markers of bone formation and resorption. The parallel rise in markers of bone formation and resorption confirms the coupling of bone formation and resorption in Paget’s disease. The degree of bone marker elevation reflects the extent and severity of the disease. For most patients, serum total ALP remains the test of choice both for diagnosis and assessing response to therapy. Occasionally, a symptomatic patient with evidence of progression at a single site may have a normal total ALP level but increased bone-specific ALP. For unclear reasons, serum osteocalcin, another marker of bone formation, is not always elevated and is not recommended for use in diagnosis or management of Paget’s disease. In contrast, bone formation marker P1NP does reflect the activity of the disease and can be used instead of total ALP. Bone resorption markers (serum or urine N-telopeptide or C-telopeptide measured in the blood or urine) are also elevated in active Paget’s disease and decrease more rapidly in response to therapy than does ALP.

PART 12 Endocrinology and Metabolism FIGURE 424-3 Radiograph of a 73-year-old man with Paget’s disease of the right proximal femur. Note the coarsening of the trabecular pattern with marked cortical thickening and narrowing of the joint space consistent with osteoarthritis secondary to pagetic deformity of the right femur. Serum calcium and phosphate levels are normal in Paget’s disease. Immobilization of a patient with active Paget’s disease may rarely cause hypercalcemia and hypercalciuria and increase the risk for nephrolithiasis. However, the discovery of hypercalcemia, even in the presence of immobilization, should prompt a search for another cause of hypercalcemia. In contrast, hypocalcemia or mild secondary hyper parathyroidism may develop in Paget’s patients with very active bone formation and insufficient calcium and vitamin D intake, particularly during bisphosphonate therapy when bone resorption is rapidly sup pressed and active bone formation continues. Therefore, adequate calcium and vitamin D intake should be instituted prior to administration of bisphosphonates. TREATMENT Paget’s Disease of Bone The

development of effective and potent pharmacologic agents (Table 424-1) has changed the treatment philosophy from treating only symptomatic patients to treating asymptomatic patients who are at risk for complications. According to the Endocrine Society Clinical Practice Guidelines published in 2014, pharmacologic therapy is indicated for most patients with active Paget's disease who are at risk of complications. Treatment may be initiated to control symptoms caused by metabolically active Paget's disease such as bone pain, fracture, headache, pain from pagetic radicu lopathy or arthropathy, or neurologic complications; to decrease local blood flow and minimize operative blood loss in patients TABLE 424-1 Pharmacologic Agents Approved for Treatment of Paget's Disease NORMALIZATION OF ALKALINE PHOSPHATASE (ALP) DOSE AND MODE OF DELIVERY NAME Zoledronic acid 5 mg IV over 15 min 90% of patients at 6 mo Pamidronate 30 mg/d IV over 4 h on 3 days ~50% of patients Risedronate 30 mg/d PO for 2 mo 73% of patients Alendronate 40 mg/d PO for 6 mo 63% of patients Tiludronate 800 mg/d PO for 3 mo 35% of patients Etidronate 200–400 mg/d PO × 6 mo 15% of patients Calcitonin (Miacalcin) 100 U SC daily for 6–18 mo (may reduce to 50 U 3× per week) (Reduction of ALP by up to 50%)

who need surgery at an active pagetic site; to reduce hypercalciuria that may occur during immobilization; and to decrease the risk of complications when disease activity is high (elevated ALP) and when the site of involvement involves weight-bearing bones, areas adjacent to major joints, vertebral bodies, and the skull. Whether or not early therapy prevents late complications remains to be deter mined. Randomized studies from the United Kingdom showed no difference in bone pain, fracture rates, quality of life, and hearing loss between patients who received pharmacologic therapy to con trol symptoms (bone pain) and those receiving bisphosphonates to normalize serum ALP. However, the conclusions of these studies are debatable since the majority of subjects had already received bisphosphonate therapy in the past, perhaps limiting generalizabil ity, and because the bone deformities that occur with Paget's disease may take many years to manifest. It seems likely that the restoration of normal bone architecture following suppression of pagetic activ ity will prevent further deformities and complications. Agents approved for treatment of Paget's disease suppress the very high rates of bone resorption and secondarily decrease the high rates of bone formation (Table 424-1). As a result of decreas ing bone turnover, pagetic structural patterns, including areas of poorly mineralized woven bone, are replaced by more nor mal cancellous or lamellar bone. Reduced bone turnover can be documented by a decline in serum formation markers (ALP and P1NP) and urine or serum resorption markers (N-telopeptide, C-telopeptide). Bisphosphonates are the mainstay of pharmacologic therapy of Paget's disease. Among them, zoledronic acid is currently recom mended as the first choice, particularly for those who have severe disease or need rapid normalization of bone turnover (neurologic symptoms, severe bone pain due to a lytic lesion, risk of an impend ing fracture, or pretreatment prior to elective surgery in an area of active disease). Zoledronic acid normalized bone turnover faster and in a high proportion of patients (>90%) than oral bisphos phonates with the therapeutic effect persisting for months or even years. It is given at a dose of 5 mg as an intravenous infusion over 20 min, although slower rates of infusion are recommended for elderly or those with mild impairment of renal function. More sig nificant renal impairment (glomerular filtration rate <35 mL/min) is a contraindication for use of zoledronic acid due to higher risk of further deterioration of renal function. About 20–25% of patients experience a flulike syndrome after the first infusion, which can be partly ameliorated by pretreatment with acetaminophen, non steroidal anti-inflammatory drugs (NSAIDs), or glucocorticoids. Oral bisphosphonates, alendronate and risedronate, can be used in subjects who have mild disease or some degree of renal impairment.

Oral bisphosphonates should be taken first thing in the morning on an empty stomach, followed by maintenance of upright posture with no food, drink, or other medications for 30–60 min. The efficacy of different agents, based on their ability to normalize or decrease ALP levels, is summarized in Table 424-1, although the response rates are not comparable because they are obtained from different studies. The subcutaneous injectable form of salmon calcitonin is approved for the treatment of Paget's disease but is rarely used due to its low potency and should be reserved for patients who either do not tolerate bisphosphonates or have a contraindication to their use. For patients with contraindication to bisphosphonates, another alternative is denosumab, an antibody to RANKL, which has been reported to result in reduction in ALP. However, it has not been approved for this indication and has less complete and less durable effects than bisphosphonates. SCLEROSING BONE DISORDERS ■ ■OSTEOPETROSIS Osteopetrosis refers to a group of disorders caused by severe impair ment of osteoclast-mediated bone resorption. Other terms that are often used include marble bone disease, which captures the solid x-ray

appearance of the involved skeleton, and Albers-Schonberg disease, which refers to the milder, adult form of osteopetrosis also known as autosomal dominant osteopetrosis type II. The major types of osteope trosis include malignant (severe, infantile, autosomal recessive) osteo petrosis and benign (adult, autosomal dominant) osteopetrosis types I and II. A rare autosomal recessive intermediate form has a more benign prognosis. Autosomal recessive carbonic anhydrase (CA) II deficiency produces osteopetrosis of intermediate severity associated with renal tubular acidosis and cerebral calcification. Etiology and Genetics Naturally occurring and gene-knockout animal models with phenotypes similar to those of the human dis orders have been used to explore the genetic basis of osteopetrosis. The primary defect in osteopetrosis is the loss of osteoclastic bone resorption and preservation of normal osteoblastic bone forma tion. Osteoprotegerin (OPG) is a soluble decoy receptor that binds osteoblast-derived RANK ligand, which mediates osteoclast differ entiation and activation (Fig. 424-1). Transgenic mice that overex press OPG develop osteopetrosis, presumably by blocking RANK ligand. Mice deficient in RANK lack osteoclasts and develop severe osteopetrosis. Recessive mutations of CA II prevent osteoclasts from generat ing an acid environment in the clear zone between its ruffled bor der and the adjacent mineral surface. Absence of CA II, therefore, impairs osteoclastic bone resorption. Other forms of human disease have less clear genetic defects. About one-half of the patients with malignant infantile osteopetrosis have a mutation in the TCIRG1 gene encoding the osteoclast-specific subunit of the vacuolar proton pump, which mediates the acidification of the interface between bone mineral and the osteoclast ruffled border. Mutations in the CLCN7 chloride channel gene cause autosomal dominant osteopetrosis type II. A drug-induced version of osteopetrosis has been reported in children with osteogenesis imperfecta who receive repeated doses of bisphosphonates. Clinical Presentation The incidence of autosomal recessive severe (malignant) osteopetrosis ranges from 1 in 200,000 to 1 in 500,000 live births. As bone and cartilage fail to undergo modeling, paralysis of one or more cranial nerves may occur due to narrowing of the cranial foramens. Failure of skeletal modeling also results in inadequate mar row space, leading to extramedullary hematopoiesis with hypersplen ism and pancytopenia. Hypocalcemia due to lack of osteoclastic bone resorption may occur in infants and young children. The untreated infantile disease is fatal, often before age 5. Adult (benign) osteopetrosis is an autosomal dominant disease that is usually diagnosed by the discovery of typical skeletal changes in young adults who undergo radiologic evaluation of a fracture. The prevalence is 1 in 100,000 to 1 in 500,000 adults. The course is not always benign, because fractures may be accompanied by loss of vision, deafness, psychomotor delay, mandibular

osteomyelitis, and other complications usually associated with the juvenile form. In some kindred, nonpenetrance results in skip generations, while in other families, severely affected children are born into families with benign disease. The milder form of the disease does not usually require treatment. Radiography Typically, there are generalized symmetric increases in bone mass with thickening of both cortical and trabecular bone. Diaphyses and metaphyses are broadened, and alternating sclerotic and lucent bands may be seen in the iliac crests, at the ends of long bones, and in vertebral bodies. The cranium is usually thickened, particularly at the base of the skull, and the paranasal and mastoid sinuses are underpneumatized. Laboratory Findings The only significant laboratory findings are elevated serum levels of osteoclast-derived tartrate-resistant acid phosphatase (TRAP) and the brain isoenzyme of creatine kinase. Serum calcium may be low in severe disease, and parathyroid hormone and 1,25-dihydroxyvitamin D levels may be elevated in response to hypocalcemia.

TREATMENT Osteopetrosis Allogeneic human leukocyte antigen (HLA)–identical bone mar row transplantation has been successful in some children. Fol lowing transplantation, the marrow contains progenitor cells and normally functioning osteoclasts. With long-term follow-up after transplantation, radiographic improvements, such as improvements in Erlenmeyer flask deformities, are seen, although there is not complete normalization. A cure is most likely when children are transplanted before age 4. Marrow transplantation from nonidenti cal HLA-matched donors has a much higher failure rate. Limited studies in small numbers of patients have suggested variable benefits following treatment with interferon γ-1β, 1,25-dihydroxyvitamin D (which stimulates osteoclasts directly), methylprednisolone, and a low-calcium/high-phosphate diet. Paget’s Disease and Other Dysplasias of Bone CHAPTER 424 Surgical intervention is indicated to decompress optic or audi tory nerve compression. Orthopedic management is required for the surgical treatment of fractures and their complications, includ ing malunion and postfracture deformity. ■ ■PYKNODYSOSTOSIS This is an autosomal recessive form of osteosclerosis that is believed to have affected the French impressionist painter Henri de ToulouseLautrec. The molecular basis involves mutations in the gene that encodes cathepsin K, a lysosomal metalloproteinase highly expressed in osteoclasts and important for bone-matrix degradation. Osteoclasts are present but do not function normally. Pyknodysostosis is a form of short-limb dwarfism that presents with frequent fractures but usually a normal life span. Clinical features include short stature; kyphosco liosis and deformities of the chest; high arched palate; proptosis; blue sclerae; dysmorphic features including small face and chin, frontooccipital prominence, pointed beaked nose, large cranium, and obtuse mandibular angle; and small, square hands with hypoplastic nails. Radiographs demonstrate a generalized increase in bone density, but in contrast to osteopetrosis, the long bones are normally shaped. Sepa rated cranial sutures, including the persistent patency of the anterior fontanel, are characteristic of the disorder. There may also be hypopla sia of the sinuses, mandible, distal clavicles, and terminal phalanges. Persistence of deciduous teeth and sclerosis of the calvarium and base of the skull are also common. Histologic evaluation shows normal cortical bone architecture with decreased osteoblastic and osteoclastic activities. Serum chemistries are normal, and unlike osteopetrosis, there is no anemia. There is no known treatment for this condition, and there are no reports of attempted bone marrow transplant. ■ ■PROGRESSIVE DIAPHYSEAL DYSPLASIA Also known as Camurati-Engelmann disease, progressive diaphyseal dysplasia is an autosomal dominant disorder that is characterized radio graphically by diaphyseal hyperostosis and a symmetric thickening and increased diameter of the endosteal and periosteal surfaces of the diaphyses of the long bones, particularly the femur and

tibia, and, less often, the fibula, radius, and ulna. The genetic defect responsible for the disease has been localized to the area of chromosome 19q13.2 encoding transforming growth factor (TGF)-β1. The mutation promotes activa tion of TGF-β1. The clinical severity is variable. The most common pre senting symptoms are pain and tenderness of the involved areas, fatigue, muscle wasting, and gait disturbance. The weakness may be mistaken for muscular dystrophy. Characteristic body habitus includes thin limbs with little muscle mass yet prominent and palpable bones and, when the skull is involved, large head with prominent forehead and proptosis. Patients may also display signs of cranial nerve palsies, hydrocephalus, central hypogonadism, and Raynaud's phenomenon. Radiographi cally, patchy progressive endosteal and periosteal new bone formation is observed along the diaphyses of the long bones. Bone scintigraphy shows increased radiotracer uptake in involved areas. Treatment with low-dose glucocorticoids relieves bone pain and may reverse the abnormal bone formation. Intermittent bisphosphonate

therapy has produced clinical improvement in a limited number of patients. Disease activity may also attenuate as patients enter adulthood.

■ ■HYPEROSTOSIS CORTICALIS GENERALISATA This is also known as van Buchem's disease; it is an autosomal recessive disorder characterized by endosteal hyperostosis in which osteosclero sis involves the skull, mandible, clavicles, and ribs. The major manifes tations are due to narrowed cranial foramens with neural compressions that may result in optic atrophy, facial paralysis, and deafness. Adults may have an enlarged mandible. Serum ALP levels may be elevated, which reflect the uncoupled bone remodeling with high osteoblastic formation rates and low osteoclastic resorption. As a result, there is increased accumulation of normal bone. Endosteal hyperostosis with syndactyly, known as sclerosteosis, is a more severe form. The genetic defects for both sclerosteosis and van Buchem's disease have been asso ciated with mutations in the SOST gene. PART 12 Endocrinology and Metabolism ■ ■MELORHEOSTOSIS Melorheostosis (Greek, "flowing hyperostosis") may occur sporadically or follow a pattern consistent with an autosomal recessive disorder. The major manifestation is progressive linear hyperostosis in one or more bones of one limb, usually a lower extremity. The name comes from the radiographic appearance of the involved bone, which resembles melted wax that has dripped down a candle. Symptoms appear during childhood as pain or stiffness in the area of sclerotic bone. There may be associated ectopic soft tissue masses, composed of cartilage or osse ous tissue, and skin changes overlying the involved bone, consisting of scleroderma-like areas and hypertrichosis. The disease does not prog ress in adults, but pain and stiffness may persist. Laboratory tests are unremarkable. Somatic mutations in MAP2K1, which increases MEK1 activity downstream of the RAS pathway, and SMAD3, which upregu lates the TGF-β/SMAD pathway, have been identified in affected bone in patients with melorheostosis. There is no specific treatment. Surgical interventions to correct contractures are often unsuccessful. ■ ■OSTEOPOIKILOSIS The literal translation of osteopoikilosis is "spotted bones"; it is a benign autosomal dominant condition in which numerous small, vari ably shaped (usually round or oval) foci of bony sclerosis are seen in the epiphyses and adjacent metaphyses. The lesions may involve any bone except the skull, ribs, and vertebrae. They may be misidentified as metastatic lesions. The main differentiating points are that bony lesions of osteopoikilosis are stable over time and do not accumulate radionucleotide on bone scanning. In some kindred, osteopoikilosis is associated with connective tissue nevi known as dermatofibrosis lenticularis disseminata, also known as Buschke-Ollendorff syndrome. Most cases are caused by mutations in LEMD3, which is involved with bone morphogenetic protein (BMP) signaling. Histologic inspection

reveals thickened but otherwise normal trabeculae and islands of nor mal cortical bone. No treatment is indicated. ■ ■HEPATITIS C–ASSOCIATED OSTEOSCLEROSIS Hepatitis C–associated osteosclerosis (HCAO) is a rare acquired dif fuse osteosclerosis in adults with prior hepatitis C infection. After a latent period of several years, patients develop diffuse appendicular bone pain and a generalized increase in bone mass with elevated serum ALP. Bone biopsy and histomorphometry reveal increased rates of bone formation, decreased bone resorption with a marked decrease in osteoclasts, and dense lamellar bone. One patient had increased serum OPG levels, and bone biopsy showed large numbers of osteoblasts positive for OPG and reduced osteoclast number. Empirical therapy includes pain control, and there may be beneficial response to bisphos phonate. Long-term antiviral therapy may reverse the bone disease. DISORDERS ASSOCIATED WITH DEFECTIVE MINERALIZATION ■ ■HYPOPHOSPHATASIA This is a rare inherited disorder that presents as rickets in infants and children or osteomalacia in adults with paradoxically low serum levels of ALP. The frequency of the severe neonatal and infantile forms is

about 1 in 100,000 live births in Canada, where the disease is most common because of its high prevalence among Mennonites and Hut terites. It is rare in African Americans. The severity of the disease is remarkably variable, ranging from intrauterine death associated with profound skeletal hypomineralization at one extreme to premature tooth loss as the only manifestation in some adults. Severe cases are inherited in an autosomal recessive manner, but the genetic patterns are less clear for the milder forms. The disease is caused by a deficiency of tissue nonspecific (bone/liver/kidney) ALP (TNSALP), which, although ubiquitous, results only in bone abnormalities. Protein levels and functions of the other ALP isozymes (germ cell, intestinal, pla cental) are normal. Defective ALP permits accumulation of its major naturally occurring substrates including phosphoethanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal 5′-phosphate (PLP). The accumulation of PPi interferes with mineralization through its action as a potent inhibitor of hydroxyapatite crystal growth. Perinatal hypophosphatasia becomes manifest during pregnancy and is often complicated by polyhydramnios and intrauterine death. The infantile form becomes clinically apparent before the age of 6 months with failure to thrive, rachitic deformities, functional craniosynostosis despite widely open fontanels (which are actually hypomineralized areas of the calvarium), raised intracranial pressure, and flail chest with predisposition to pneumonia. Hypercalcemia and hypercalciuria are common. This form has a mortality rate of ~50%. Prognosis seems to improve for the children who survive infancy. Childhood hypophos phatasia has variable clinical presentation. Premature loss of decidu ous teeth (before age 5) is the hallmark of the disease. Rickets causes delayed walking with waddling gait, short stature, and dolichocephalic skull with frontal bossing. The disease often improves during puberty but may recur in adult life. Adult hypophosphatasia presents during middle age with painful, poorly healing metatarsal stress fractures or thigh pain due to femoral pseudofractures. Presentation may be subtle with muscle pain or recurring headaches as the predominant symp toms. It is important to recognize hypophosphatasia in adults because treatment with bisphosphonates can result in increased rather than decreased bone fragility. Laboratory investigation reveals low ALP levels and normal or elevated levels of serum calcium and phosphorus despite clinical and radiologic evidence of rickets or osteomalacia. Serum parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels are normal. The elevation of PLP is specific for the disease and may even be present in asymptomatic parents of severely affected children. Because vitamin B6 increases PLP levels, vitamin B6 supplements should be discontinued 1 week before testing. Clinical testing is avail able to detect loss-of-function mutation(s) within the ALPL gene that encodes TNSALP. In contrast to

other forms of rickets and osteomalacia, calcium and vitamin D supplementation should be avoided because they may aggra vate hypercalcemia and hypercalciuria. A low-calcium diet, glucocor ticoids, and calcitonin have been used in a small number of patients with variable responses. Because fracture healing is poor, placement of intramedullary rods is best for acute fracture repair and for pro phylactic prevention of fractures. In 2015, asfotase alfa, a TNSALP, was approved as enzyme replacement therapy for the perinatal/ infantile- and juvenile-onset forms. With 7 years of therapy, children with perinatal/infantile forms showed sustained improvements in mineralization, along with improvements in other features, such as respiratory function and growth. In adolescents and adults, 5 years of therapy demonstrated improved functional abilities, such as increases in 6-min walk time. ■ ■AXIAL OSTEOMALACIA This is a rare disorder characterized by defective skeletal mineraliza tion despite normal serum calcium and phosphate levels. Clinically, the disorder presents in middle-aged or elderly men with chronic axial skeletal discomfort. Cervical spine pain may also be present. Radio graphic findings are mainly osteosclerosis due to coarsened trabecu lar patterns typical of osteomalacia. Spine, pelvis, and ribs are most commonly affected. Histologic changes show defective mineralization

and flat, inactive osteoblasts. The primary defect appears to be an acquired defect in osteoblast function. The course is benign, and there is no established treatment. Calcium and vitamin D therapies are not effective. ■ ■FIBROGENESIS IMPERFECTA OSSIUM This is a rare condition of unknown etiology. It presents in both sexes; in middle age or later; and with progressive, intractable skeletal pain and fractures; worsening immobilization; and a debilitating course. The only biochemical abnormality is elevated ALP. Radiographic evaluation reveals generalized osteomalacia, osteopenia, and occa sional pseudofractures. Histologic features include a tangled pattern of collagen fibrils with abundant osteoblasts and osteoclasts. Use of growth hormone led to substantial short-term clinical improvement in two adult patients, but long-term outcomes are unknown. No other effective treatment is known. Spontaneous remission has been reported in a small number of patients. FIBROUS DYSPLASIA AND

MCCUNE-ALBRIGHT SYNDROME Fibrous dysplasia is a sporadic disorder characterized by the presence of one (monostotic) or more (polyostotic) expanding fibrous skeletal lesions composed of bone-forming mesenchyme. The association of the polyostotic form with café au lait spots and hyperfunction of an endocrine system such as pseudoprecocious puberty of ovarian origin is known as McCune-Albright syndrome (MAS). A spectrum of the phenotypes is caused by activating mutations in the GNAS1 gene, which encodes the α subunit of the stimulatory G protein (Gsα). As the postzygotic mutations occur at different stages of early development, the extent and type of tissue affected are variable and explain the mosaic pattern of skin and bone changes. GTP binding activates the Gsα regu latory protein and mutations in regions of Gsα that selectively inhibit GTPase activity, which results in constitutive stimulation of the cyclic AMP–protein kinase A signal transduction pathway. Such mutations of the Gsα protein–coupled receptor may cause autonomous function in bone (parathyroid hormone receptor); skin (melanocyte-stimulating hormone receptor); and various endocrine glands including ovary (follicle-stimulating hormone receptor), thyroid (thyroid-stimulating hormone receptor), adrenal (adrenocorticotropic hormone receptor), and pituitary (growth hormone–releasing hormone receptor). The skeletal lesions are composed largely of mesenchymal cells that do not differentiate into osteoblasts, resulting in the formation of imperfect bone. In some areas of bone, fibroblast-like cells develop features of osteoblasts in that they produce extracellular matrix that organizes into woven bone. Calcification may occur in some

areas. In other areas, cells have features of chondrocytes and produce cartilage-like extracellular matrix. Clinical Presentation Fibrous dysplasia occurs with equal fre quency in both sexes, whereas MAS with precocious puberty is more common (10:1) in girls. The monostotic form is the most common and is usually diagnosed in patients between 20 and 30 years of age without associated skin lesions. The polyostotic form typically mani fests in children <10 years old and may progress with age. Early-onset disease is generally more severe. Lesions may become quiescent in puberty and progress during pregnancy or with estrogen therapy. In polyostotic fibrous dysplasia, the lesions most commonly involve the maxilla and other craniofacial bones, ribs, and metaphyseal or diaphyseal portions of the proximal femur or tibia. Expanding bone lesions may cause pain, deformity, fractures, and nerve entrapment. Sarcomatous degeneration involving the facial bones or femur is infrequent (<1%). The risk of malignant transformation is increased by radiation, which has proven to be ineffective treatment. In rare patients with widespread lesions, renal phosphate wasting and hypo phosphatemia may cause rickets or osteomalacia. Hypophosphatemia may be due to production of a phosphaturic factor by the abnormal fibrous tissue. MAS patients may have café au lait spots, which are flat, hyper pigmented skin lesions that have rough borders (“coast of Maine”)

Paget’s Disease and Other Dysplasias of Bone CHAPTER 424 FIGURE 424-4 Radiograph of a 16-year-old male with fibrous dysplasia of the right proximal femur. Note the multiple cystic lesions, including the large lucent lesion in the proximal midshaft with scalloping of the interior surface. The femoral neck contains two lucent cystic lesions. in contrast to the café au lait lesions of neurofibromatosis that have smooth borders (“coast of California”). The most common endocri nopathy is isosexual pseudoprecocious puberty in girls. Other less common endocrine disorders include thyrotoxicosis, Cushing’s syn drome, acromegaly, hyperparathyroidism, hyperprolactinemia, and pseudoprecocious puberty in boys. Radiographic Findings In long bones, the fibrous dysplastic lesions are typically well-defined, radiolucent areas with thin cortices and a ground-glass appearance. Lesions may be lobulated with trabecu lated areas of radiolucency (Fig. 424-4). Involvement of facial bones usually presents as radiodense lesions, which may create a leonine appearance (leontiasis osea). Expansile cranial lesions may narrow foramens and cause optic lesions, reduce hearing, and create other manifestations of cranial nerve compression. Laboratory Results Serum ALP is occasionally elevated, but calcium, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels are normal. Patients with extensive polyostotic lesions may have hypophosphatemia, hyperphosphaturia, and osteomalacia. The hypophosphatemia and phosphaturia are directly related to the levels of fibroblast growth factor 23 (FGF23). Biochemical markers of bone turnover may be elevated. TREATMENT Fibrous Dysplasia and MAS Spontaneous healing of the lesions does not occur, and there is no established effective treatment. Improvement in bone pain and partial or complete resolution of radiographic lesions have been reported after IV bisphosphonate therapy. Deno sumab given monthly or every 3 months is effective in reducing bone turnover markers and leads to some clinical improvement, though subsequent discontinuation of denosumab occasionally results in hypercalcemia. Surgical stabilization is used to pre vent pathologic fracture or destruction of a major joint space and to relieve nerve root or cranial nerve compression or sinus obstruction.

OTHER DYSPLASIAS OF BONE

AND CARTILAGE

■ ■PACHYDERMOPERIOSTOSIS Pachydermoperiostosis, or hypertrophic osteoarthropathy (primary or idiopathic), is an autosomal dominant disorder characterized by periosteal new bone formation that involves the distal extremities. The lesions present as clubbing of the digits and hyperhidrosis and thickening of the skin, primarily of the face and forehead. The changes usually appear during adolescence, progress over the next decade, and then become quiescent. During the active phase, progressive enlarge ment of the hands and feet produces a paw-like appearance, which may be mistaken for acromegaly. Arthralgias, pseudogout, and limited mobility may also occur. The disorder must be differentiated from secondary hypertrophic osteopathy that develops during the course of serious pulmonary disorders. The two conditions can be differentiated by standard radiography of the digits in which secondary pachydermo periostosis has exuberant periosteal new bone formation and a smooth and undulating surface. In contrast, primary hypertrophic osteopathy has an irregular periosteal surface. PART 12 Endocrinology and Metabolism The disease is genetically heterogeneous and is related to increases in prostaglandin E2. Synovial fluid does not have an inflammatory profile. There is no specific therapy, although a limited experience with colchicine suggests some benefit in controlling the arthralgias. ■ ■OSTEOCHONDRODYSPLASIAS These include several hundred heritable disorders of connective tissue. These primary abnormalities of cartilage manifest as disturbances in cartilage and bone growth. Selected growth-plate chondrodysplasias are described here. For discussion of chondrodysplasias, see Chap. 425. Achondrodysplasia This is a relatively common form of shortlimb dwarfism that occurs in 1 in 15,000 to 1 in 40,000 live births. The disease is caused by a mutation of the fibroblast growth factor receptor 3 (FGFR3) gene that results in a gain-of-function state. Most cases are sporadic mutations. However, when the disorder appears in families, the inheritance pattern is consistent with an autosomal dominant disorder. The primary defect is abnormal chondrocyte proliferation at the growth plate that causes development of short, but proportionately thick, long bones. Other regions of the long bones may be relatively unaffected. The disorder is manifest by the presence of short limbs (particularly the proximal portions), normal trunk, large head, saddle nose, and an exaggerated lumbar lordosis. Severe spinal deformity may lead to cord compression. The homozygous disorder is more serious than the sporadic form and may cause neonatal death. Vosoritide, an analog of C-type natriuretic peptide, increased growth among children in phase 3 clinical trials and was approved in 2021. Treatment is controversial among patient support communities. Infigratinib, a selective FGFR1-3 tyrosine kinase inhibitor, is in clinical trials. Pseudoachondroplasia clinically resembles achondrodysplasia but has no skull abnormalities. Enchondromatosis This is also called dyschondroplasia or Ollier’s disease; it is also a disorder of the growth plate in which the primary cartilage is not resorbed. Cartilage ossification proceeds normally, but it is not resorbed normally, leading to cartilage accumulation. The changes are most marked at the ends of long bones, where the highest growth rates occur. Chondrosarcoma develops infrequently. The asso ciation of enchondromatosis and cavernous hemangiomas of the skin and soft tissues is known as Maffucci’s syndrome. Both Ollier’s disease and Maffucci’s syndrome are associated with various malignancies, including granulosa cell tumor of the ovary and cerebral glioma. Multiple Osteochondromas This is also called multiple exostoses or diaphyseal aclasis; it is a genetic disorder that follows an autosomal dominant pattern of inheritance. In this condition, areas of growth plates become displaced, presumably by growing through a defect in the perichondrium. The lesion begins with vascular invasion of the growth-plate cartilage, resulting in a characteristic radiographic finding of a mass that is in direct communication with the marrow cavity of the parent bone. The underlying cortex is resorbed. The disease is caused

by inactivating mutations of the EXT1 and EXT2 genes, whose prod ucts normally synthesize heparan sulfate chains. The resulting heparan sulfate deficiency impacts signaling pathways and leads to ectopic chon drogenesis. Solitary or multiple lesions are located in the metaphyses of long bones. Although usually asymptomatic, the lesions may interfere with joint or tendon function or compress peripheral nerves. The lesions stop growing when growth ceases but may recur during pregnancy. There is a small risk for malignant transformation into chondrosarcoma. Palovarotene, a retinoic acid receptor agonist, is in clinical trials. EXTRASKELETAL (ECTOPIC) CALCIFICATION AND OSSIFICATION Deposition of calcium phosphate crystals (calcification) or formation of true bone (ossification) in nonosseous soft tissue may occur by one of three mechanisms: (1) metastatic calcification due to a supranormal calcium × phosphate concentration product in extracellular fluid; (2) dystrophic calcification due to mineral deposition into metaboli cally impaired or dead tissue despite normal serum levels of calcium and phosphate; and (3) ectopic ossification, or true bone formation. Disorders that may cause extraskeletal calcification or ossification are listed in Table 424-2. ■ ■METASTATIC CALCIFICATION Soft tissue calcification may complicate diseases associated with significant hypercalcemia, hyperphosphatemia, or both. In addition, vitamin D and phosphate treatments or calcium administration in the presence of mild hyperphosphatemia, such as during hemodialysis, may induce ectopic calcification. Calcium phosphate precipitation may complicate any disorder when the serum calcium × phosphate concentration product is >75. The initial calcium phosphate deposition is in the form of small, poorly organized crystals, which subsequently organize into hydroxyapatite crystals. Calcifications that occur in hypercalcemic states with normal or low phosphate have a predilection for kidney, lungs, and gastric mucosa. Hyperphosphatemia with nor mal or low serum calcium may promote soft tissue calcification with predilection for the kidney and arteries. The disturbances of calcium and phosphate in renal failure and hemodialysis are common causes of soft tissue (metastatic) calcification. ■ ■TUMORAL CALCINOSIS This is a rare genetic disorder characterized by masses of metastatic calcifications in soft tissues around major joints, most often shoulders, hips, and ankles. Tumoral calcinosis differs from other disorders in that the periarticular masses contain hydroxyapatite crystals or amorphous calcium phosphate complexes, whereas in fibrodysplasia ossificans pro gressiva (below), true bone is formed in soft tissues. About one-third of tumoral calcinosis cases are familial, with both autosomal recessive and autosomal dominant modes of inheritance reported. The disease is also associated with a variably expressed abnormality of dentition marked TABLE 424-2 Diseases and Conditions Associated with Ectopic Calcification and Ossification Metastatic calcification Hypercalcemic states Primary hyperparathyroidism Sarcoidosis Vitamin D intoxication Milk-alkali syndrome Renal failure Hyperphosphatemia Tumoral calcinosis Secondary hyperparathyroidism Pseudohypoparathyroidism Renal failure Hemodialysis Cell lysis following chemotherapy Therapy with vitamin D and Dystrophic calcification Inflammatory disorders Scleroderma Dermatomyositis Systemic lupus erythematosus Trauma-induced Ectopic ossification Myositis ossificans Postsurgery Burns Neurologic injury Other trauma Fibrodysplasia ossificans progressiva phosphate

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