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 radiographically 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 tumor growth factor (TGF) β1. The mutation promotes activation of TGF-β1. The clinical severity is variable. The most common presenting 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. Radiographically, 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.

HYPEROSTOSIS CORTICALIS GENERALISATA

This is also known as *van Buchem's disease*; it is an autosomal recessive disorder characterized by endosteal hyperostosis in which osteosclerosis involves the skull, mandible, clavicles, and ribs. The major manifestations 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 assigned to the same region of the chromosome 17q12-q21. It is possible that both conditions may have deactivating mutations in the *BEER* (bone-expressed equilibrium regulator) gene.

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 osseous tissue, and skin changes overlying the involved bone, consisting of scleroderma-like areas and hypertrichosis. The disease does not progress in adults, but pain and stiffness may persist. Laboratory tests are unremarkable. No specific etiology is known. 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, variably 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*. Histologic inspection reveals thickened but otherwise normal trabeculae and islands of normal cortical bone. No treatment is indicated.

HEPATITIS C–ASSOCIATED OSTEOSCLEROSIS

Hepatitis C–associated osteosclerosis (HCAO) is a rare acquired diffuse 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 bisphosphonate. 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 Hutterites. 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, placental) 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 about 50%. Prognosis seems to improve for the children who survive infancy. Childhood hypophosphatasia has variable clinical presentation. Premature loss of deciduous 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.

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 B_6 increases PLP levels, vitamin B_6 supplements should be discontinued 1 week before testing. Clinical testing is available to