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Edward F. McCarthy and Frank J. Frassica
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Chapter 1

Diagnosing bone disease

The spectrum of skeletal disease

Looking at bones in a museum or a gross anatomy teaching box may leave the impression they are inert, rock-like substances. However, this is not true. Bones are alive and dynamic just like other tissues. They atrophy if they are not used; they become infected; they die if deprived of blood; they develop neoplasms; they respond to systemic changes; and they heal themselves.

Considering these dynamic reactions, bone diseases should be conceptualized like diseases of other body systems. Therefore, an initial approach to diagnosing a skeletal disorder is to place the lesion in one of seven major disease categories. These categories, which are common to all diseases, are congenital, metabolic, traumatic, reactive, circulatory, neoplastic, infectious, and changes due to systemic disease (Table 1–1). In some cases, choosing the correct category is the first step to making the correct diagnosis. In other cases, the disease category is known only after the correct diagnosis has been made. Because understanding these categories is essential to diagnosing bone disease, we begin with a brief summary. Detailed discussions of these categories will be presented in subsequent chapters.

Congenital diseases

The first category of bone disease, those due to gene mutations, usually manifest in childhood. These congenital diseases affect the skeleton either directly or indirectly. A direct effect on the skeleton is caused by mutations in any of the huge number of genes which control the growth and development of bone or cartilage. These disorders are called the **skeletal dysplasias**, and at least 456 have been defined.[1] In addition to gene mutations which affect the skeleton directly, mutations in genes which regulate other tissues, such as the reticuloendothelial system, affect bones indirectly. Of the approximately 8000 known single gene disorders, at least 600 either directly or indirectly affect the skeleton. Despite this large number of disease entities, congenital bone diseases are uncommon in general clinical practice.

Skeletal dysplasias (gene mutations directly affecting the skeleton)

The skeletal dysplasias manifest in three principal ways: short stature, abnormally shaped bones, and skeletal fragility. For the diagnostician, an important feature of these manifestations is their symmetry in the skeleton. An asymmetric disorder is unlikely to be a skeletal dysplasia.

Recognizing the abnormal size and shape of bones (and whether the changes are symmetrical) is best done with plain radiographs. In fact, the nomenclature of the skeletal dysplasias, although always in a continuous state of flux, is based almost exclusively on radiographic features – which bones and bone segments are involved. Therefore, radiologists usually diagnose and classify skeletal dysplasias. Moreover, because most of these diseases are rare and the manifestations so numerous, a difficult diagnosis requires a radiologist with a special expertise in congenital bone diseases.

Whereas the skeletal dysplasias can be distinguished by plain radiographic features, their pathologic features are nonspecific. All these diseases appear very similar under the microscope. For example, a pathologist cannot distinguish, at least with routine light microscopy, an abnormal growth plate of a patient with achondroplasia from one with pseudoachondroplasia. Moreover, in some cases, the bone or cartilage from a patient with skeletal dysplasia is histologically normal. Therefore, the diagnosis of skeletal dysplasias is not the province of the pathologist. The pathologist, however, must be familiar with these diseases to ensure that tissue is available for special

Table 1–1 The seven major bone disease categories

Congenital	Examples: achondroplasia, osteogenesis imperfecta
Metabolic	Examples: rickets, osteoporosis
Traumatic	Examples: fracture, avulsion injuries, myositis ossificans
Circulatory	Example: osteonecrosis
Neoplastic	Examples: metastatic carcinoma, osteosarcoma
Infectious	Example: osteomyelitis
Bone changes in systemic disease	Example: hypertrophic pulmonary osteoarthropathy

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studies. These include electron microscopy, tissue culture, or genetic investigations.

Although skeletal dysplasias are currently classified by radiologic features, future classification systems may be based on genetic information. Advances in molecular genetics have led to the identification of many of the mutations that cause these diseases. Every year, at least one skeletal dysplasia is elucidated by identifying its causative mutation. The first genetic bone disease to be so characterized was osteogenesis imperfecta. This disease, the most common of all the skeletal dysplasias, results in brittle bones. In 1975, a mutation in one of the two genes encoding type 1 collagen was discovered to be its cause.[2] More recently, it was discovered that achondroplasia, another common skeletal dysplasia, is caused by a mutation in the gene encoding the receptor for fibroblast growth factor.[3] Of the 456 skeletal dysplasias, 316 have been associated with mutations in 226 genes. These numbers increase every year. Identifying causative gene mutations not only results in clarifying specific diseases, it also increases the understanding of normal skeletal growth and development.

Skeletal dysplasias exhibit a wide range of clinical severity. Severe dysplasias are evident at birth or even in utero. Some of these, such as thanatophoric dysplasia, are incompatible with life. Infants die at birth from respiratory failure due to chest cage deformity. Less severe dysplasias, such as pseudoachondroplasia, become manifest in childhood. Even milder dysplasias, such as the mild variant of multiple epiphyseal dysplasia, become evident only in early adulthood with the onset of early osteoarthritis. Finally, a skeletal dysplasia, such as osteopoikilosis, may be asymptomatic throughout a patient's life.

Clinical severity also differs among patients with the same dysplasia. Recent molecular genetic discoveries suggest that in some dysplasias the varying degrees of severity are due to different point mutations in the same gene. For example, over 150 different mutations in the two genes encoding type 1 collagen have been discovered.[4] These different mutations account for the wide range of clinical presentations of osteogenesis imperfecta.

Since the skeletal dysplasias usually affect only bones and cartilage, patients have normal intelligence and a near normal life span. Most patients with these disorders lead productive lives. However, their abnormally shaped bones often lead to physical disability; some are severely handicapped. Many require orthopedic surgery to correct deformities, stabilize frequent fractures, or treat early osteoarthritis. In addition to orthopedic problems, patients with skeletal dysplasias must contend with the emotional burden of their deformities. They usually help each other with these problems. For example, Little People of America is a mutual support group with almost 10,000 members.

Gene mutations indirectly affecting the skeleton

In addition to the skeletal dysplasias, genetic diseases targeting other tissues can also affect the skeleton. For example, neurofibromatosis 1, the most common single gene disorder of humans, primarily causes neural tumors and cafe au lait spots. It can also affect bones in a variety of ways. Patients may develop scoliosis, pseudarthrosis, and bone erosions. Other genetic diseases, such as those involving the reticuloendothelial system, also affect the skeleton. In Gaucher's disease, for example, abnormal cells accumulate in the bone marrow and cause osseous lesions.

Metabolic bone disease

Whereas congenital bone disease results from gene mutations, metabolic bone disease results from alterations in the chemical environment of the body. This chemical environment consists of hormones, vitamins, minerals and other systemic factors – all interacting in complicated ways with physical activity. Disturbances in this environment adversely affect the two components of bone, calcium and the organic matrix. This causes osteopenia, a generalized decrease in skeletal mass. Thus, the characteristic feature of metabolic bone disease is weak bones. When osteopenia is severe enough to result in clinical symptoms, such as fractures or bone pain, it is called osteoporosis. Therefore, when patients present with fractures associated with little or no trauma, physicians should be alert to the likelihood of metabolic bone disease.

Osteopenia associated with endocrine disorders

Metabolic bone diseases may be grouped in three categories: problems due to endocrine disorders, osteopenia associated with aging, and disuse osteoporosis. First, of the many endocrine disorders which adversely affect the skeleton, the most damaging are those which disturb calcium homeostasis. Calcium homeostasis is critical for two reasons. First, calcium participates in many of the body's physiologic reactions, and, therefore, its serum level must be precisely regulated. Second, calcium must be available to mineralize bone.

Calcium homeostasis depends on several factors. First calcium intake must be adequate. Second, vitamin D, which gets calcium into the system, must also be present. Third, parathyroid function must be normal because parathyroid hormone regulates the serum calcium level. Finally, the interaction of these factors requires healthy kidneys. Because of the complexity of calcium homeostasis, disorders of any aspect of this system lead to metabolic bone disease. These disorders include rickets and osteomalacia, hyperparathyroidism, and renal disease. Generally, these endocrine disorders are characterized by specific histopathologic changes and can be diagnosed by looking at bone biopsies.

Osteopenia associated with aging

Osteopenia associated with aging is the second major category of metabolic bone disease. Unlike the osteopenia of endocrine disease in which calcium homeostasis is abnormal, in this category, calcium homeostasis appears normal. The osteopenia of aging is due to a reduction in the organic matrix. Also, unlike disorders of calcium homeostasis, no specific

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histopathologic features characterize osteopenia of aging. The bone is normal; there is just too little of it.

Osteopenia of aging is caused by imbalanced bone remodeling. From birth to death, the human skeleton is remodeling; old bone is gradually removed by osteoclasts, and new bone is added by osteoblasts, a process known as bone turnover. Theoretically, the remodeling process is necessary to remove bits of damaged bone. In the normal adult skeleton, the remodeling process is balanced: the amount of bone replaced equals the amount removed. However, in osteopenia of aging, the amount of bone replaced is less than the amount removed, an imbalance known as uncoupling. After multiple remodeling cycles over many years, the accumulated effect of uncoupling results in osteopenia.

There are two overlapping syndromes of age-related osteopenia: senile osteoporosis and post-menopausal osteoporosis.[5] Senile osteoporosis is a natural result of aging. After a person reaches peak skeletal mass, usually in the mid-twenties, bone mass begins to decline gradually. This age-related bone loss occurs in both men and women of all ethnic groups and cultures. In this syndrome, the bone turnover rate is normal, but uncoupling, probably due to decreased osteoblast longevity, gradually reduces bone mass.

Post-menopausal osteoporosis, by contrast, is a syndrome of rapid bone loss. Beginning at the menopause, and lasting only a few years, some women suffer a rapid bone loss which is engrafted on the normal age-related bone loss. These women are acutely sensitive to estrogen withdrawal. As a result, their bone turnover rate increases. This increased turnover rate leads to a rapid bone loss because of age-related remodeling imbalance.

These two syndromes of age-related bone loss are very common. In fact, osteoporosis is one of the most important public health problems in developed countries. Thirty percent of post-menopausal women have clinical osteoporosis.[6] Men also suffer from this disease. These women and men have suffered, or are at risk to suffer, vertebral fractures, hip fractures, or distal radius fractures. Osteoporosis accounts for 300,000 hip fractures in the United States each year. The annual cost to treat these fractures exceeds seven billion dollars.[7]

Although orthopedic surgeons treat the fractures which complicate osteoporosis, endocrinologists usually diagnose and treat the metabolic bone disease itself. Because up to 30% of bone may be lost before plain radiographic changes are evident, early osteoporosis is often difficult to diagnose.[8] Therefore, the most important diagnostic tool used by endocrinologists is the dual x-ray absorptiometry (DEXA) scan. This diagnostic modality compares a person's bone mass with a control group. In addition, a wide variety of laboratory tests are available to diagnose metabolic bone disease. These include measurements of serum hormones, vitamin D levels, and indices of bone turnover. Although prevention is crucial in managing osteoporosis, a wide variety of drugs are available to prevent further bone loss and, with lesser success, to restore bone that has been lost.

Disuse osteoporosis

The final major category of metabolic bone disease includes the osteoporotic syndromes which result from disuse. Bones need to be stressed and strained to stay healthy. Although the relationship between bone use and maintenance of bone mass is not fully understood, electrical activity in bone probably plays a vital role. Bone is minimally deformed each time it is stressed, and the deformation results in the generation of piezioelectricity and electric streaming potentials. These tiny electric currents somehow maintain balanced bone turnover. Failure to generate these currents results in increased osteoclastic resorption. For example, prolonged bed rest or long-term weightlessness results in significant generalized osteoporosis. Syndromes of focal osteoporosis also occur. For example, prolonged non-weight-bearing of one leg results in bone loss in that leg.

Traumatic bone disease

The third category of bone disease includes those disorders caused by trauma. These disorders will be discussed in detail in Chapter 5. Healthy bones can withstand stress and strain well beyond that required in daily use. However, once forces exceed this safety range, bones break. Fractures are, by far, the most common bone disease. Yet, bones have a remarkable healing ability. In fact, bone is one of the few tissues in which the healing process is so complete, the original structure so well restored, that evidence of injury is obliterated, whereas other tissues, such as liver, brain, and kidney, heal with a fibrous scar. Moreover, the bone's architecture is restored by a process of remodeling after the healing tissue, known as fracture callus, completely ossifies. Stress and strain stimulate osteoclasts and osteoblasts to sculpt the bone back to its original shape. Depending on the bone involved, a fracture takes a few weeks to a few months for the bone ends to unite. But it takes a few years for bone to remodel to its original shape.

The impetus for healing is so strong that even fractures through abnormal bone heal normally. This even includes severely osteoporotic bone. Furthermore, fracture healing is seldom adversely affected by diseases of organ systems. Only diabetes and cigarette smoking are associated with poor fracture callus formation.

However, complications occasionally occur at fracture sites. For example, a fracture may disrupt the blood supply to a portion of bone resulting in focal osteonecrosis. The dead bone cannot heal to the viable bone. A second complication is a non-union. This complication, which occurs most commonly in tibial fractures, is a failure of the fracture callus to ossify. A fibrous, rather than a bony, bridge occurs between the fractured bone ends. As a result, motion occurs at the fracture site, a condition known as a pseudarthrosis. Why does the fracture callus fail to ossify? One cause is extensive stripping of the osteogenic periosteum, a problem which occurs in particularly violent injuries or from vigorous surgical manipulation. Non-union also results if a portion of muscle or fibrous tissue becomes trapped in the fracture site. Non-unions can be

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successfully treated. Surgery is required to start the fracture over again by removing the fibrous bridge. Often internal stabilization and bone grafting are required.

Although abnormal bones heal like normal ones, they break more easily. Whereas significant trauma is required to break normal bone, abnormal bone fractures with little trauma. Fractures through bones with either focal or generalized diseases are known as pathologic fractures. For example, an aggressive lytic bone tumor greatly weakens a bone, and pathologic fractures occur. Although both primary and metastatic bone tumors cause pathologic fractures, this complication is more common in metastatic carcinoma to bone. In fact, treating or preventing pathologic fractures is one of the most important aspects of managing patients with terminal cancer. In addition to focal bone lesions, generalized bone disease also predisposes to fractures. Thus, fractures through severely osteoporotic bones are pathologic fractures. In these patients, the pathologic fracture is often the presenting symptom of the generalized disease.

Although fractures are the most common and easily recognized form of traumatic bone disease, two special types of bone injury present diagnostic problems: stress fractures and avulsion injuries. A stress fracture is the reaction of bone to repetitive trauma. Although none of the traumas by themselves is sufficient to produce injury, the cumulative effect eventually weakens the bone. The repetitive stress stimulates a zone of increased bone remodeling, and a discrete line of rarefaction – the stress fracture – occurs. Typically, a patient who develops a stress fracture has taken up a new activity, such as jogging, and particular activities are associated with stress fractures in specific bones. For example, military recruits, unaccustomed to long marches, develop metatarsal stress fractures. Because stress fractures are painful and cause subtle radiographic changes, they are occasionally mistaken for neoplasms or other bone diseases. Awareness of the varied presentations of stress fractures is the key to their diagnosis.

Avulsion injuries, another manifestation of trauma, may also be mistaken for neoplasms. These injuries, most common in children, result from repetitive muscular activity which pulls off a portion of periosteum from the bone surface. Occasionally, a portion of underlying bone also is avulsed, and it is the resulting periosteal bone reaction and adjacent intraosseous or soft tissue edema which mimics a neoplasm. This problem most frequently occurs on the medial femoral condyle. However, avulsion injuries can occur anywhere a tendon is attached to bone.

Circulatory diseases

The fourth category of bone disease which we summarize here includes disorders resulting from disturbances in blood circulation. We will discuss these in detail in Chapter 7. Bone is a richly vascular tissue; it receives 20% of the cardiac output. The blood supply to bone comes from many sources: large nutrient arteries that penetrate the diaphysis, smaller arteries which enter the epiphysis and metaphysis, and many small arterioles which penetrate the cortex from the periosteum. Focal bone death, the most common circulatory disease, results from disruption of blood flow of any of these vessels. Histologic changes which follow bone death are known as osteonecrosis.

Bone dies when blood flow is disrupted. This happens in one of three clinical settings: fracture, infection, or intravascular occlusion. The first setting, fracture, causes bone death by rupture or compression of an artery. Such injuries occur if the fracture is severely displaced or if there has been an associated joint dislocation. For example, osteonecrosis of the femoral head may occur after a displaced femoral neck fracture. Other bones particularly susceptible to fracture-related osteonecrosis are the talus and the carpal navicular.

The second setting in which bone death may occur is infection. Spreading inflammatory tissue isolates a segment of bone by surrounding it with a purulent exudate and isolating it from its blood supply. The dead bone fragment, known as a sequestrum, harbors causative microorganisms and protects them against the body's defenses and antibiotics. The sequestra must be removed to allow the infection to heal.

The third setting of osteonecrosis is a variety of clinical conditions which predispose to intravascular occlusion. Vascular occlusion is followed by infarction of the bone supplied by that vessel. However, unlike other organs, such as the brain or the heart, in which infarction is due to atherosclerosis, bone infarction is usually due to intravascular coagulation. This process occurs most frequently at either end of the femur and results in distinct clinical syndromes.

The most common syndrome is osteonecrosis of the femoral head. From 10,000 to 20,000 new cases of osteonecrosis of the femoral head occur in the United States each year.[9] Usually, men between the ages of 20 and 40 are affected. The clinical symptoms of this disease are due to the nearness of the osteonecrotic segment to the articular surface. Dead bone is brittle, and weight-bearing causes microfractures through the brittle trabeculae. As a result, the articular surface eventually collapses and secondary osteoarthritis develops in the joint. Affected patients usually have at least one of multiple risk factors. Risk factors include alcohol abuse, steroid therapy, and hypercoaguable blood.

Bone infection

Infection in bone is the next category of bone disease. Bone, like any other tissue, can become infected, a condition known as osteomyelitis. In fact, organisms love to grow in bone. However, osteomyelitis is difficult to diagnose. Although most patients with osteomyelitis present with systemic signs of infection, the clinical and radiographic patterns vary considerably. Due to these various presentations, osteomyelitis is known as the "great imitator." It must always be considered as a diagnostic possibility in any medullary bone lesion, particularly in children.

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Osteomyelitis occurs by two mechanisms – direct inoculation of organisms into bone and the hematogenous spread of organisms to bone from an infection elsewhere in the body. Infection from direct inoculation, known as secondary osteomyelitis, occurs most commonly after an open fracture. Prior to antibiotics, bone infection almost always complicated an open fracture. Nowadays, only 5% of open fractures become infected.

Hematogenous osteomyelitis, known as primary osteomyelitis, is usually a pediatric disease.[10] Children present acutely with symptoms of infection: fever, pain, and leucocytosis. Radiographs reveal bone destruction and a periosteal reaction, usually in the metaphysis of a long bone. The cause of these bone changes is the proliferation of granulation tissue with varying amounts of an acute purulent exudate. Staphylococcus aureus is the usual causative organism. Adults may, on occasion, develop acute osteomyelitis. In adults, the spine is the most common site. Usually, they have had prior genitourinary tract manipulation or they are immunocompromised.

Acute osteomyelitis must be diagnosed and treated decisively. Otherwise, organisms gain a foothold, in part facilitated by the bone's reactive response which tends to protect the organisms. Incomplete eradication of acute osteomyelitis, a problem which occurs in 5% of cases, leads to chronic osteomyelitis. Unfortunately, chronic osteomyelitis is extremely difficult, and sometimes impossible, to cure. Chronic osteomyelitis is characterized by the long-term interaction, usually for decades, of the bone and the infecting organism. Periodic flare-ups occur, and radiographs show ill-defined areas of radiolucency mixed with areas of increased density. The radiodense areas are the bone's reactions to the infection. In addition, radiodense sequestra (dead bone fragments) appear in the lucent areas. Extensive surgical debridement and antibiotic therapy is required to treat chronic osteomyelitis.

Although most bone infections are caused by bacteria, any type of microorganism can cause osteomyelitis. For example, fungal and mycobacterial organisms can infect bone, particularly in immunocompromised patients. In addition, viruses and parasites, such as the echinococcal worm, cause unusual presentations. Therefore, the orthopedist must culture a suspected osteomyelitic lesion for all organisms.

Neoplastic bone disease

Bone neoplasms are generally divided into two major categories – those which arise in bones, known as primary bone tumors, and those which have metastasized to bone from neoplasms elsewhere. Primary bone tumors may be benign or malignant. Metastatic bone tumors are always malignant, and they indicate an advanced stage of cancer.

Metastatic lesions in bone are extremely common. This is due to the high incidence of cancer in developed countries (it is the second leading cause of death) and the natural history of the disease. Most people dying of cancer have bone metastases. Therefore, any patient with a bone lesion who is over age 40 should be presumed to have metastatic cancer until proven otherwise. Although any malignant tumor can spread to bone, carcinomas of the lung, breast, and prostate account for 80% of bone metastases.

Unlike the distinctive radiographic features of most other bone lesions, metastatic carcinoma in bone has a wide range of radiographic patterns. This variability occasionally makes diagnosis difficult. Lesions may be radiodense (blastic metastases) or radiolucent (lytic metastases). Lesions may be well defined or poorly defined, and they may be centered in the medullary canal or on the bone surface. Despite their variable radiographic presentations, however, metastatic carcinomas occur in predictable locations. They usually develop in the axial skeleton and are most common in the spine. Other sites frequently involved are the pelvis, proximal femurs, and proximal humeri. Metastatic carcinoma is rare in the distal extremities. Although metastatic carcinoma may present in one site, most patients develop multiple lesions.

Two clinical settings characterize metastatic carcinoma to bone. First, some patients with a bone lesion have no history of a primary carcinoma. In these patients, the diagnosis of metastasis requires a search for the primary site. Unfortunately, the site of the primary cannot always be discerned from the histopathologic features of the metastasis. Therefore, finding the primary is a clinical and radiographic problem. Sometimes it is never found.

The second, and more common, presentation of bone metastases occurs in a patient with a known primary. In these patients, the diagnosis of metastasis establishes the advanced stage of the disease. Orthopedists must direct their attention to the prevention or treatment of pathologic fractures, a common complication of metastatic lesions in bone. These procedures are moderately successful in relieving pain and restoring function for the remainder of the patient's life, usually not more than 2 years.

After metastatic carcinoma in bone, multiple myeloma is the most common bone neoplasm. There are about 13,800 new cases per year in the United States. Multiple myeloma is a neoplastic proliferation of plasma cells which almost always presents with bone lesions. Although plasma cells are not native to the bone marrow, multiple myeloma is considered a primary bone neoplasm because most of the neoplastic cells are in the bone marrow. However, other organs are also affected.

Multiple myeloma affects older adults; usually patients are over age 50. Unlike many other neoplastic proliferations, multiple myeloma has a very insidious onset. In the early stages, bone lesions, almost always multiple, are difficult to see with plain radiographs. In fact, diffuse osteopenia may be the only radiographic feature. As the disease progresses, punched-out osseous lesions begin to appear. Patients develop pain and, occasionally, pathologic fractures.

In almost all cases of multiple myeloma (98%), the neoplastic plasma cells retain their function – they synthesize and secrete immunoglobulins. However, because the neoplastic

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plasma cells originate from a single cell, the immunoglobulins are monoclonal. These monoclonal immunoglobulins can be recognized in a serum protein electrophoresis. In addition to monoclonal serum immunoglobulins, monoclonal light chains are excreted in the urine. Recognition of these serum and urine protein abnormalities aids in the diagnosis of multiple myeloma. Therefore, serum proteins should be studied in any elderly patient with an undiagnosed lytic bone lesion.

Although multiple myeloma is usually a disseminated bone disease, a solitary lesion is present in 5–10% of cases. This manifestation of myeloma, known as solitary myeloma, occurs in slightly younger patients. In addition, serum protein abnormalities are less common (50–75% of cases). About half the patients with solitary plasmacytoma eventually develop disseminated disease.

Unlike metastatic bone tumors, which originate in organs other than bone, primary tumors begin in bone. Several important features characterize primary bone tumors. First, primary bone tumors exhibit a wide spectrum of tissue differentiation. There are about 20 different types, and many types have well-defined variants. Generally, these lesions are grouped according to the major pattern of tissue differentiation. Thus, there are cartilage lesions, fibrous lesions, and bone forming lesions with benign and malignant versions of each. In addition to these major categories of differentiation, some tumors, such as giant cell tumor and Ewing sarcoma, are of uncertain differentiation. These lesions are regarded as specific entities.

The second important characteristic of primary bone tumors is the age of affected patients. Unlike metastatic tumors or myeloma, which are diseases of older people, primary bone tumors predilect adolescents and young adults. The probable cause of this age predilection is the susceptibility of growing or modeling bone to neoplastic transformation. Those bone areas which are most active are most vulnerable. Thus, the distal femur and proximal tibia are the most common locations for primary bone tumors.

The third characteristic of primary bone tumors is that they each have specific radiographic presentations. In general, each type of lesion favors a certain zone of a bone, and each type has very distinctive radiographic features. In many instances, the diagnosis can be made by radiographic features alone. In addition, some of the specific variants of lesions are defined solely by radiographic features. Therefore, when a biopsy is required, awareness of the radiographic features is critical to making the correct diagnosis. Thus, primary bone tumors may be regarded as radiographic–pathologic entities.

The final general characteristic of primary bone tumors is their wide variety of clinical behavior. Some lesions are benign and grow slowly. In fact, some tumors are not neoplasms at all. For example, enchondromas and osteochondromas are developmental lesions (hamartomas) that cease growing after full skeletal maturation. Other bone tumors are difficult to classify as benign or malignant. For example, giant cell tumor is very aggressive locally but only rarely metastasizes. If it does, the metastases are slow growing and are therefore regarded as "benign metastasis." Finally, some primary bone tumors, such as Ewing sarcoma, are highly malignant. Patients with these neoplasms, despite recent therapeutic advances, have a poor prognosis.

Bone changes in systemic disease

The final category of bone disorders includes various skeletal manifestations of systemic disease. Although bone changes in these diseases are usually diffuse and symmetric, focal lesions occasionally occur. Bone change in systemic disease manifests in two manners. In some cases, bone changes are the initial presentation of an underlying systemic disease. In other cases, the systemic disease is long-standing, and the bone changes are noted incidentally.

The most common systemic conditions that affect bone are diseases of the kidney and the hematologic or reticuloendothelial systems. Chronic renal failure is always complicated by widespread bone changes. These changes, known as renal osteodystrophy, are particularly exaggerated in patients on renal dialysis. The changes of renal osteodystrophy may become so severe that the nephrologist must pay constant attention to minimizing this disease when caring for patients with renal failure. Bone changes in renal disease are due to the impairment of the kidney's ability to regulate calcium and phosphorus metabolism. Therefore, renal osteodystrophy may be regarded as a metabolic bone disease.

Hematologic disorders also produce bone changes, but they are usually diagnosed incidentally during long-term patient care. These changes are usually due to expansion of the marrow. For example, leukemic infiltration of the marrow causes widespread lytic lesions. Similarly, anemias characterized by marrow hyperplasia, such as iron-deficiency anemia and thalassemia, also expand the bone marrow space and produce widespread symmetric lytic changes. Some hematologic disorders, however, such as myeloproliferative disease and systemic mastocytosis, produce bone sclerosis.

Unlike the diffuse, symmetrical bone changes of hematologic disorders, proliferative disorders of the reticuloendothelial system tend to produce multifocal and asymmetric lesions. Bone lesions occur in these disorders because cells of the reticuloendothelium system, mainly macrophages and histiocytes, reside in the bone marrow. Proliferative disorders of histiocytes include sarcoidosis, Langerhan's histiocytosis, and sinus histiocytosis with massive lymphadenopathy. In contrast to the anemias, bone changes in reticuloendothelial disease are often the presenting problem.

Diseases of other organ systems also involve bone. For example, neuropathic arthropathy occurs in many patients with neurologic disorders, particularly those with diabetic neuropathy. Chronic pulmonary disease also affects bones. Patients with long-standing lung disease develop extensive deposits of periosteal new bone, a condition called pulmonary

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hypertrophic osteoarthropathy. In this disorder, chronic hypoxia results in subperiosteal vascular proliferation and new bone formation. Clubbing of the fingers, also a feature of chronic lung disease, is probably caused by the same mechanism.

The multidisciplinary approach to diagnosis

The diagnosis and management of bone disease depends on the close teamwork of the clinician, the radiologist, and the pathologist. This team must consider a bone lesion's clinical presentation, radiographic image, and histomorphology in order to determine the lesion's behavior and plan effective treatment. Before making a specific diagnosis, the team must answer the following questions about the lesion's behavior: "What is it doing to the patient?" Specifically, "Is the lesion growing?" If so, "How fast?" By answering these questions, a more important one can be asked: "What is the lesion going to do to the patient in the future?" Pondering these questions before making a specific diagnosis allows the team to get a feel for the lesion. After sensing the lesion's behavior, a specific diagnosis is more likely to be correct.

Three principal sources of information are crucial to the process of judging a lesion's behavior: its clinical presentation, laboratory studies, and the practice of radiographic histologic correlation. In addition, anallary radiographic and histologic techniques permit more specific diagnoses.

The clinical presentation

The clinical presentation of a bone lesion offers numerous clues to its behavior and helps place it in one of the disease categories we have just summarized. Important considerations are age of the patient, location of the lesion, pain, swelling and deformity, the presence of other disease, and systemic symptoms.

Age and location

Although any lesion can occur at just about any age, most bone lesions predilect certain age groups. For example, eosinophilic granuloma usually occurs in children and should always be included in the differential diagnosis of lytic lesions in this age group. By contrast, a lytic lesion in an older adult is a metastatic carcinoma or plasmacytoma until proven otherwise.

Location is also a diagnostic clue. Many lesions, particularly neoplasms, occur almost exclusively in certain zones of a bone. For example, nonossifying fibroma occurs only in the metaphysis of long bones. Therefore, this diagnosis should never be rendered for a benign fibrous lesion in other locations, such as the skull or spine. Another lesion, giant cell tumor, almost always involves the epiphysis. Therefore, giant cell-containing lesions in other locations are unlikely to be giant cell tumors. Lesions also favor particular bones. For example, unicameral bone cysts occur most frequently in the proximal humerus, and osteoblastomas favor the spine. Thus, knowing the sites of predilection of the various bone diseases is crucial to accurate diagnosis.

When multiple lesions are present, their distribution is extremely important. Symmetrically distributed lesions, such as the sclerotic foci of osteopoikilosis, usually indicate a systemic or congenital disease, whereas asymmetrically distributed lesions, such as the sclerotic foci of metastatic prostatic carcinoma, often indicate a neoplasm.

Pain

Pain usually indicates that a lesion is growing. Conversely, non-growing lesions are almost always painless. The pain from growing lesions results from the stimulation of small, unmyelinated nerves in haversian canals or from expansion of the periosteum. Bone pain is a dull aching pain, similar to a toothache, and is characteristically worse at night. The duration of bone pain is a clue to how long a lesion has been growing.

Although growing bone lesions are painful, the clinician must decide if the patient's pain is being caused by the lesion or by something else. Often, a painful joint calls attention to a nearby, unrelated bone lesion. For example, an MRI exam to study degenerative changes in the knee or shoulder occasionally reveals a nearby cartilage lesion. Usually, the lesion is a non-growing enchondroma which, in the absence of joint pain, would go unnoticed. Two features help distinguish joint pain from bone pain. First, unlike bone pain, joint pain eases at night or with immobilization of the joint. Second, joint pain disappears with an intraarticular injection of an analgesic. If pain persists after these procedures, it is most likely caused by the bone lesion.

On rare occasions, non-growing lesions are painful, particularly when they occur in weight-bearing bones. In these situations, pain is almost always due to stress fractures through the lesion. For example, enchondromas and healing nonossifying fibromas, although non-growing, weaken the bone. As a result, increased activity causes painful intralesional stress fractures and simulates a growing process. In these situations, an MRI often contributes to overdiagnosis. This is because a soft tissue signal increase due to hemorrhage or edema from the stress fracture may be mistaken for neoplastic tissue. In this setting, the clue to the presence of a stress fracture is the disappearance of pain with non-weight-bearing. An orthopedist who is aware of this complication of non-growing lesions, is less likely to do unnecessary surgery.

Swelling and deformity

Swelling and deformity are also clues to the nature of a bone lesion. Swelling is usually caused by the expansion of a surface lesion, such as a parosteal osteosarcoma or an osteochondroma. The duration and rate of swelling usually reflect the speed of the lesion's growth. However, bursae often form over surface lesions, particularly osteochondromas. Inflammation in these bursae increases their size, a change which may be interpreted as rapid growth of the underlying

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lesion. Therefore, the orthopedist should compare the amount of clinical swelling with the radiographs to avoid misinterpretation.

Deformity produced by bone lesions is best evaluated by radiographs. However, certain skeletal alterations may be appreciated clinically. One alteration is limb-length discrepancy. In children, lesions near the epiphyseal plate may either stimulate or retard bone growth. The amount of discrepancy often indicates the duration of the lesion.

Other diseases and systemic signs

Another question in the evaluation of a bone lesion is whether or not it is a manifestation of disease in another organ system. Because the skeleton is sensitive to many systemic factors, a careful history must be taken. Renal, endocrine, hematologic, and pulmonary disease all may influence the skeleton. The presence of disease in any one of these systems may immediately explain the bone lesion.

Systemic signs are also an important clue to the behavior of a bone lesion. The most important systemic signs are those caused by infection. The presence or history of fever suggests that a bone lesion may be osteomyelitis. High fevers are caused by acute osteomyelitis; low-grade or intermittent fevers characterize chronic osteomyelitis. Also, a history of a remote febrile illness may be a clue to subacute osteomyelitis. In the presence of fever, a leucocytosis or an elevated erythrocyte sedimentation rate increases the suspicion of bone infection.

Although fever usually indicates osteomyelitis, other bone lesions, on rare occasions, also cause fever. For example, rapidly growing neoplasms, such as Ewing sarcoma, may produce fever and leucocytosis. This is because rapid growth results in extensive tumor necrosis and the release of pyrogens into the circulation. Therefore, because Ewing sarcoma and acute osteomyelitis also have overlapping radiographic features, these two lesions may be difficult to distinguish clinically and radiographically. Sometimes even a biopsy does not solve this diagnostic dilemma. A tissue sample from a necrotic portion of a Ewing sarcoma may be histologically mistaken for infection. Awareness of the potential hazards in distinguishing Ewing sarcoma and acute osteomyelitis is important in making the correct diagnosis.

Laboratory studies

In addition to evaluating the white blood count and erythrocyte sedimentation to rule out infection, other laboratory studies are important in the diagnosis of a bone disease. For example, a complete blood count is necessary to evaluate the health of the bone marrow. Diffuse infiltrative disorders and the osteosclerotic bone dysplasias may present with anemia. Another important laboratory study is the serum protein electrophoresis. This study, necessary for the diagnosis of myeloma, should be performed in any older adult with an undiagnosed lytic bone lesion.

Indices of bone turnover

An important group of laboratory tests, ordered mainly by endocrinologists, are the indices of bone turnover.[11] These tests are useful to confirm the diagnosis of a high-turnover bone disease. These diseases may focally involve the skeleton, such as Paget's disease, or they may be diffuse, such as primary hyperparathyroidism or renal osteodystrophy. The indices of bone turnover are measurements of products which reach the serum or urine as a result of osteoblastic and osteoclastic activity. These products are increased in high-turnover bone diseases. Markers of osteoblastic activity are serum alkaline phosphatase and serum osteocalcin. Osteoblasts secrete alkaline phosphatase simultaneously with the secretion of osteoid. Although its exact function is unknown, alkaline phosphatase probably either initiates or facilitates mineralization. The other marker of osteoblastic activity, osteocalcin, is a non-collagenous component of osteoid, but, like alkaline phosphatase, its function in osteoid is unknown. Because from 10 to 25% of the synthesized osteocalcin escapes into the circulation, the serum levels reflect the amount of osteoid synthesized.[12]

Markers of osteoclastic activity include tartrate resistant acid phosphatase, urinary hydroxyproline, and urinary pyridinium crosslinks. Acid phosphatase is secreted by osteoclasts during bone resorption. Although various other tissues, including prostate and spleen, demonstrate acid phosphatase activity, only osteoclast acid phosphatase is tartrate resistant. Therefore, elevated serum levels indicate increased bone resorption.[13] Urinary hydroxyproline and urinary pyridinium crosslinks, the other markers of bone resorption, are breakdown products of collagen. Hydroxylation of proline occurs after collagen synthesis and is necessary for helix formation of the collagen molecules. Hydroxyproline is almost exclusively limited to collagen, and when bone collagen is degraded by osteoclasts during resorption, it is excreted in the urine. Increased urinary levels, therefore, indicate increased collagen breakdown, an indication of increased resorption.[14] In addition to the hydroxylation of proline, another post-translational collagen modification is the covalent crosslinking between lysines or hydroxylysines. These crosslinks resist degradation during collagen breakdown. After breakdown, the collagen fragments, held together by these crosslinks, form a molecule known as pyridinium, which is excreted in the urine. Like hydroxyproline, increased urinary levels indicate increased bone resorption.[15] A more recent index of collagen breakdown is the serum measurement of C-telopeptides.[16] These telopeptides are the terminal peptides on the collagen molecules. This very sensitive index can be measured on serum as well as urine.

Radiologic–histologic correlation

The plain radiograph represents the gross pathology of bone and joint disease and provides essential clues to the behavior of a lesion. In fact, some bone diseases can be diagnosed with certainty with plain radiographs alone. When a biopsy is necessary, the plain radiographs teach the pathologist how to

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interpret the slides. Therefore, it is not enough to simply look up the radiology report on the hospital computer. Pathologists must examine the radiographs themselves. Also, the clinician and radiologist should come to the pathology department to look at the slides with the pathologist. This sort of communication across disciplinary boundaries results in more accurate diagnosis and better treatment.

Studying the plain radiographs is the most effective way to learn what a bone lesion is doing to the patient. They reveal how long a lesion has been present and, in many cases, what type of tissue it is made of. The best way to study a plain radiograph is through histopathologic lenses.[17–19] That is, the radiologist must imagine what the lesion looks like under the microscope. This approach is most effective when considering the two major categories of radiographic patterns: patterns of radiodensity and patterns of radiolysis.[20]

Patterns of radiodensity

Radiodensity is produced by calcium. Therefore, increased radiodensity in a bone or new radiodensity on the bone surface is due to a lesion with extra or new calcium. The histologic manner of the calcium deposition is discernible by plain radiographs, and the radiologist can, therefore, diagnose what type of tissue is present. Calcium is deposited in three manners: as amorphous calcium, as calcified cartilage, or as bone. Determining which manner of calcification is present is the first step in diagnosing a radiodense lesion.

Amorphous calcification, especially on the bone surface, causes round or oval radiodensities which may be likened to a mass of squashed wet cotton balls (Fig. 1–1). Generally, each oval is uniformly radiodense. The histologic correlate of this pattern of calcification is amorphous calcified debris in soft tissue, often with an extensive histiocytic and foreign body giant cell reaction (Fig. 1–2). The calcium is either amorphous calcium phosphate or plates and laminated spherules (psammona bodies) of calcium hydroxyapatite. The calcifications are deeply basophilic and are not birefringent in polarized light. In the soft tissues adjacent to the bone, this pattern of calcification characterizes a disease called tumoral calcinosis. Intraosseous amorphous calcification also occurs, particularly in bone infarcts. In this setting, calcified fat necrosis causes ill-defined densities resembling smoke rings (Fig. 1–3). Histologically, this type of calcification occurs in necrotic fat (Fig. 1–4).

Hyaline cartilage calcification is the second major pattern of radiodensity. Cartilage is a radiolucent substance. Therefore, some intramedullary cartilage lesions are entirely radiolytic. However, as cartilage matures, calcifications appear. Typically, hyaline cartilage calcification appears as fine stipples and small

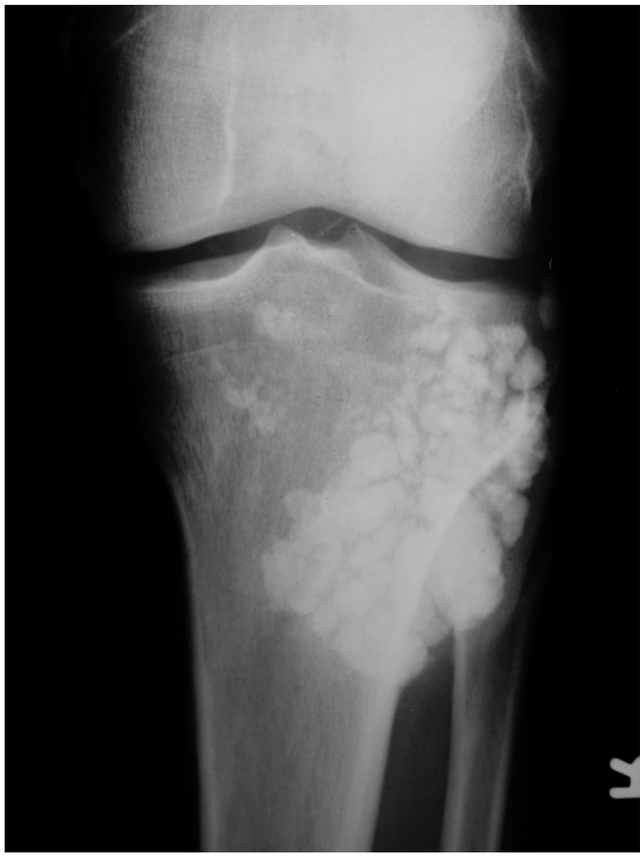

Fig. 1–1: Plain radiograph of the amorphous calcification of tumoral calcinosis.

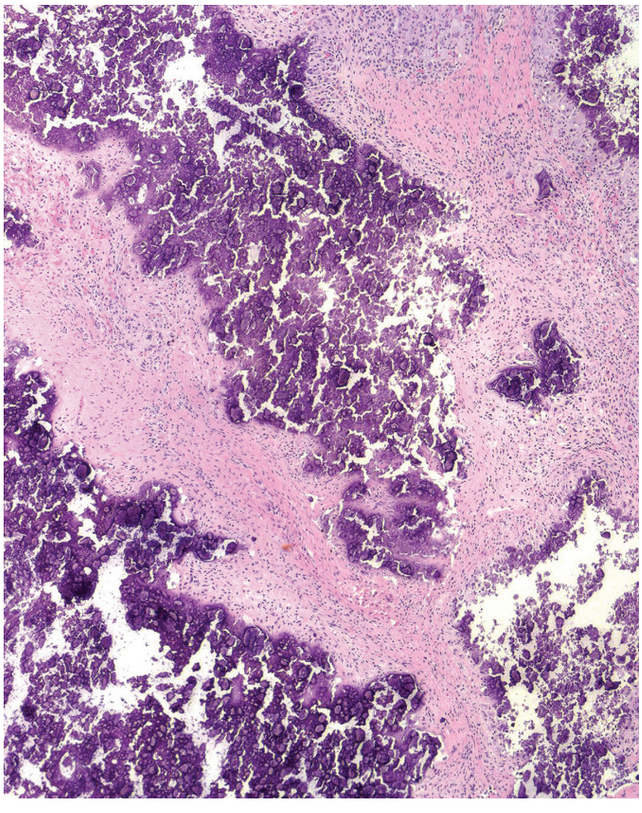

Fig. 1–2: Histology of amorphous calcification. There is amorphous basophilic powder as well as plates of calcium hydroxyapatite crystals.

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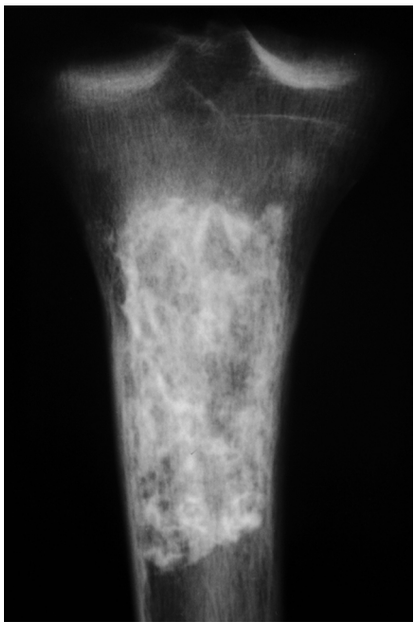

Fig. 1–3: Specimen radiograph of an infarct of proximal tibia. There is calcification of the necrotic marrow forming a smoke-ring pattern.

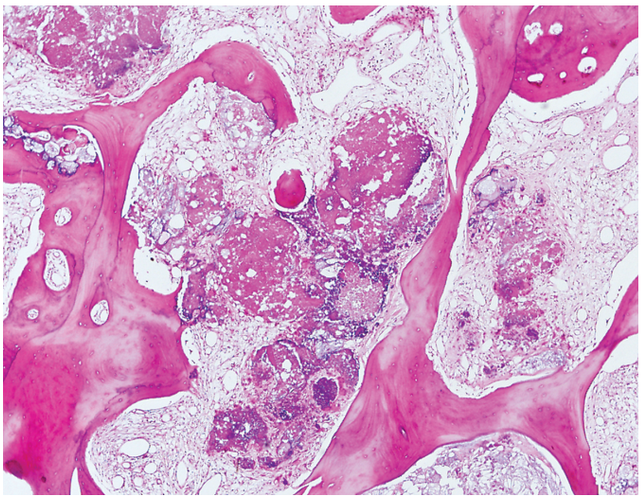

Fig. 1–4: Photomicrograph of a bone infarct showing amorphous calcification of necrotic fat.

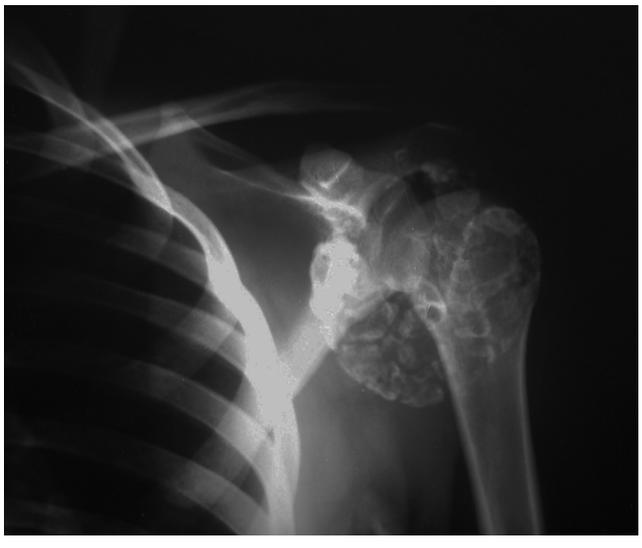

Fig. 1–5: Plain radiograph ring-shaped radiodensities of a synovial chondromatosis.

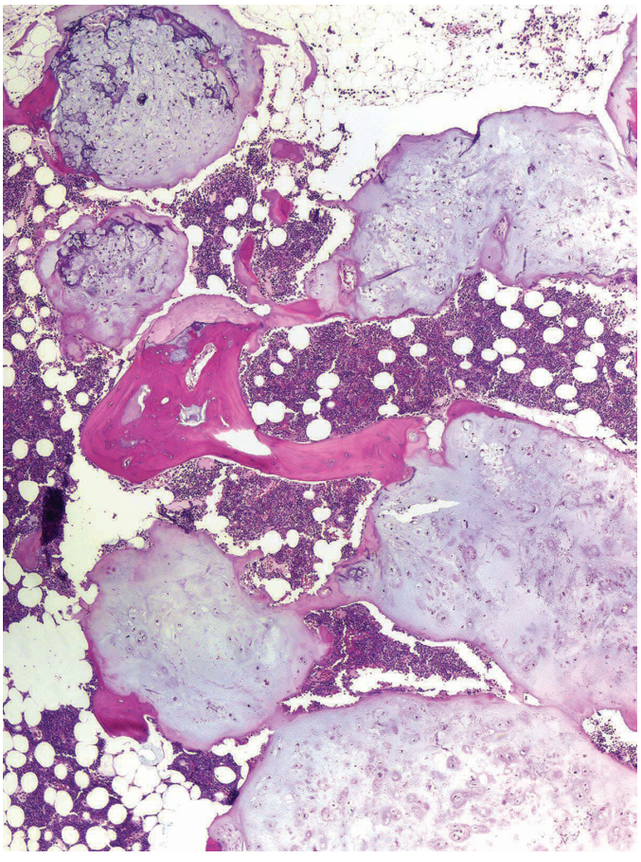

Fig. 1–6: Photomicrograph showing the lobular growth pattern of cartilage.

rings, a result of the growth characteristics of cartilage (Fig. 1–5). The clonal proliferation of chondrocytes results in discrete cartilage lobules which undergo a series of programmed changes (Fig. 1–6). First, the center of each lobule calcifies, and a group of these focally calcified lobules produces radiographic stippling. Then, the periphery of each lobule undergoes endochondral ossification (Fig. 1–7). As a result, rimming of each lobule with bone causes ring-shaped densities on plain radiographs. This pattern of calcification – rings and stipples – occurs in both surface and intramedullary hyaline cartilage lesions.

The third pattern of radiodensity is due to **bone formation**. Radiographically, bone formation is characterized by trabecular lines, most evident in surface or soft tissue osseous lesions (Fig. 1–8). Trabeculae of woven or lamellar bone are present histologically (Fig. 1–9). Although less distinct than surface lesions, extra bone is also recognizable in intramedullary bone forming lesions. Extra intramedullary bone usually manifests

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