This work is dedicated to the memory of my Mother and Father, and by the secretary of the New York Bone Club to its past and present members

Lauren V. Ackerman 1979 – 1993
Andrew Huvos 1979 – 1996
Alex Norman 1979 – 2004
Hubert A. Sissons 1979 – 1990
Leon Sokoloff 1979 – 1999
German C. Steiner 1979 –
Si-Kwang (Sam) Liu 1980 – 2003
Aquilles Villacin 1980 –
Leonard B. Kahn 1980 –
Howard D. Dorfman 1985 –
Michael J. Klein 1994 –
Harry Lumerman 1997 –
Nogah Haramati 2003 –
George Nomikos 2003 –
Benjamin Hoch 2003 – 2008
Mark A. Edgar 2003 – 2008

And many more, whose names on Earth are dark,
But whose transmitted effluence cannot die
So long as fire outlives the parent spark,

from Adonais
by Percy Bysshe Shelley (1792 – 1822)
Contributors

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Preface

I graduated from medical school in 1956. At that time, the standard texts in basic orthopaedics, physiology, pathology, and medicine provided little or no information with regard to the pathophysiology of bone and joint disease. Even as late as 1970 when I had the temerity to suggest to the Chief of the Trauma Service at a world famous medical school that perhaps we could learn something from studying bone biopsies from old ladies who had fractured their hips, my suggestion was met with incredulity. Today osteoporosis is recognized as one of the most serious problems facing the aging population.

Our own interest in, and understanding of, disease depends especially upon our teachers and colleagues. In this respect I was most fortunate in being accepted for a residency in anatomic pathology at the Beth Israel Hospital in Boston, where there was a strong tradition of intellectual exchange between the various hospitals and medical schools in the city. This was followed by a two-year fellowship at the Hospital for Joint Disease, New York, with Dr. Henry Jaffe whose whole life had been dedicated to orthopedic pathology in that great institution.

Four years spent in the department of Orthopedic Surgery at the University of Oxford exposed me to one of the most creative and imaginative orthopedic surgeons of his generation, Professor Jose Trueta, as well as two of the brightest young minds of British orthopedics at that time, Mr. Michael Freeman and Mr. John Goodfellow. In 1968 at the invitation of Dr. Philip Wilson Sr., I came to the Hospital for Special Surgery in New York City.

Much of the ever increasing sophistication in the diagnosis of bone and joint disease, I believe, owe to the foundation in 1972 of the International Skeletal Society, which, for the first time, provided a wider venue for the discussion of the radiographic and histologic diagnosis of bone and joint disease. From its inception this society was interdisciplinary, drawing its members from the leading exponents of radiology, pathology, orthopaedics, and rheumatology in the Americas, Europe, Asia, and Australia. As a result of the annual meetings tremendous progress in diagnostic acumen has been achieved and disseminated through both very successful annual refresher courses offered by the society, and its journal – Skeletal Radiology.

The foundation in 1979 of a local New York Bone Club has provided a level of intellectual fellowship for which I am profoundly grateful. Our monthly meetings over the past 30 years have taught me more of my profession than I would have ever thought possible.

This text was first published in 1984 and was intended to provide a concise, yet lavishly illustrated and comprehensive introduction to the pathology of bone and joint disorders. The target audience was trainees in orthopaedics, radiology, and pathology. Orthopaedic Pathology was one of the early textbooks to be published in full color and this I believe helped to make an understanding of the subject under discussion much more accessible to those whose daily work did not involve the use of the microscope.

Using various imaging techniques, the radiologist may observe the virtual morbid anatomic changes associated with musculoskeletal disease. The histologist in his intent to interpret tissue sections is helped considerably by both clinical and radiologic correlation; without such correlation, serious mistakes are possible. With these thoughts in mind, in the illustration of the conditions under discussion, I have tried to make use of the various imaging techniques now available, and a splendid chapter, written for the nonspecialist by Professor Judith Adams and her colleague Dr. Sarah Jackson, on imaging techniques, interpretation, and strategies is included in the text.

Most of the gross photographs and photomicrographs used in the book were taken over the many years of my professional life. Many of the clinical radiographs are from the Radiology Department at the Hospital for Special Surgery, and I thank all the members of that department for their assistance especially Drs. Robert Freiberger, Robert Schneider, and Douglas Mintz. Additional illustrations have been generously contributed by numerous colleagues throughout the world, mostly members of the International Skeletal Society, to whom I am extremely grateful.

Line drawings have been used to indicate specific features in photographs, and where the three-dimensional or temporal aspects of a structure must be shown, color schematic drawings or anatomic drawings are provided.

The bibliography is arranged by chapter, and subdivided by disease. Nowadays the availability of the internet obviates the need for exhaustive bibliographies. So I have focused on including older references that have been useful to me and that may be less accessible via the internet.

In preparation of the first edition of this book, I was fortunate to have the assistance of Dr. Vincent Vigorita, who had just completed his fellowship at Memorial Hospital before joining our staff as assistant pathologist. For the second edition, I had the invaluable help of Dr. Rafael Castro. For this as well as the third and fourth editions, Dr. Philip Rusli, who has been with the pathology department for the past eighteen years, has been my amanuensis. With his organizational skills, he has managed the logistics of cataloguing illustrations, checking references, tracking down radiographs, and many, many other tasks that are entailed in such a project as this. I am extremely grateful to him for all his help and support. Many of the images in this edition have benefitted from the expert Photoshop editing of Mr. Percy Addo-Yobo, a young Ghanese student lately working in our department.

I am indebted to my colleagues, the physicians, surgeons, and technical staff of the Pathology Department at the Hospital for Special Surgery – both past and present and especially Drs. Philip Wilson, Manjula Bansal, Edward DiCarlo, Adele Boskey, Stephen Doty, and Cathleen Raggio for their never failing support in this and other projects over the years. I am most grateful to Dr. Mark Edgar for his careful reading of the text, and his invaluable contributions and suggestions for its improvement. Finally, I thank my friends on the staff of Elsevier, especially William Schmitt and Andrea Vosburgh, for the care and hard work that went into the preparation of this book for publication.
Normal Skeletal Structure and Development
First and foremost, bone, cartilage, ligaments, and tendons have a mechanical function: providing protection, movement, and stability. Unlike the parenchymal organs, which are composed mainly of cellular elements with a metabolic function, the connective tissues are mostly formed of an extracellular matrix that is formed of materials to resist the tensile and compressive forces to which they are subjected.

The microscopic examination of bone dates back to the earliest days of microscopy. In 1691, Clopton Havers published his *Osteologia Nova*, in which he described the pores in the cortical bone that we now refer to as haversian canals (Fig. 1-1). Since then, major contributions to the study of bone anatomy and histology have been made by many of the most famous names in medicine. In 1733, Cheselden published the *Osteographia*, which contained full and accurate descriptions of all human bones gained with the use of the camera obscura (Fig. 1-2), and in 1754, the beautiful and accurate work of Albinus on bone and muscle established a new standard in anatomic illustrations.

The experiments of Haller in 1763 contributed greatly to the understanding of bone formation, and in 1772, Hunter did much to elucidate the mechanism of bone growth, particularly its appositional growth rather than that of interstitial growth such as occurs in other organ systems (Fig. 1-3). Bichat, in the early 1800s, stressed the importance of the material tissue elements shared among the different organ systems (hence histology) and, in particular, described the synovial membrane. Virchow, the father of modern pathology, wrote classic descriptions of several bone tumors and metabolic disturbances (Fig. 1-4).

**Matrix**

Some knowledge of the matrix constituents is essential to the understanding of connective tissue diseases. The various types of collagen account for 70% of all body proteins and are the principal extracellular constituents of connective tissue (Table 1-1). Type I collagen is the most common form of collagen and the major collagen found in skin, fascia, tendon, and bone. Type I collagen is made up of bundles of fibrils, which, in turn, are composed of stacked molecules formed from polypeptide chains arranged in a triple...
helical pattern (Figs. 1-5 and 1-6). At least 29 distinct types of collagen composed of at least 43 genetically distinct chains are now known, and these types vary both in size and configuration. Some contain interrupted helical structures aligned in a staggered array to form fibrils. There are also nonfiber-forming collagens, which have varying functions such as binding sites for other matrix components (type IX) or the regulation of vascularization (type X) or fiber size (type XI) (Fig. 1-7).

Hyaline cartilage has a unique type of collagen, type II, which is structurally characterized by three identical triple helical α1(II) chains. The type II fibrillar network, which will be discussed in more detail later, is essential both for maintaining the tissue’s volume and shape as well as providing articular cartilage with its tensile strength when subjected to compressive loads.

Collagen synthesis is complex and includes both intracellular and extracellular events. During the processes of transcription and translation of the collagen genes, it is necessary that a number of intervening sequences (known as introns) are spliced out. Defects in this processing of bone type I collagen lead to either defective collagen chains or reduced amounts of collagen and the clinical disease of osteogenesis imperfecta.

The protein α-chains formed first are made up of sequences of amino acids of which glycine occupies every third position; the intervening positions are frequently occupied by either proline or lysine, which are later hydroxylated in preparation for the formation of the triple helix. (Proline and lysine hydroxylases require the presence of ascorbic acid, α-ketoglutarate, Fe^{2+} and O_{2}. In the absence of vitamin C, collagen cannot be synthesized.)

TABLE 1-1 All Collagens

<table>
<thead>
<tr>
<th>Type</th>
<th>Genes</th>
<th>Structure</th>
<th>Representative Tissues</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>COL1A1, A2</td>
<td>Fibrils</td>
<td>Skin, bone, tendon, dentin, etc.</td>
<td>Osteogenesis imperfecta, Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>II</td>
<td>COL2A1</td>
<td>Fibrils</td>
<td>Hyaline cartilage, vitreous body</td>
<td>Collagenopathy, types II and XI, spondyloepiphysial dysplasia (SED)</td>
</tr>
<tr>
<td>III</td>
<td>COL3A1</td>
<td>Fibrils</td>
<td>Skin, vessels</td>
<td>Ehlers-Danlos syndrome (EDS)</td>
</tr>
<tr>
<td>IV</td>
<td>COL4A1, A2, A3, A4, A5, A6</td>
<td>Meshwork</td>
<td>Basement membranes</td>
<td>Alport’s syndrome, porencephaly, Goodpasture’s syndrome</td>
</tr>
<tr>
<td>V</td>
<td>COL5A1, A2, A3</td>
<td>Fibrils</td>
<td>Hamster lung cell cultures, fetal membranes, skin, bone, placenta, synovial membranes</td>
<td>Ehlers-Danlos syndrome (classic type)</td>
</tr>
<tr>
<td>VI</td>
<td>COL6A1, A2, A3</td>
<td>Short chain</td>
<td>Vessels, skin, intervertebral disc, placenta, heart</td>
<td>Ulrich myopathy, Bethlem myopathy</td>
</tr>
<tr>
<td>VII</td>
<td>COL7A1</td>
<td>Long chain</td>
<td>Dermo-epidermal junction</td>
<td>EDS, epidermolysis bullosa</td>
</tr>
<tr>
<td>VIII</td>
<td>COL8A1, A2</td>
<td>Short chain</td>
<td>Descemet membrane, endothelial cells</td>
<td>Corneal dystrophies</td>
</tr>
<tr>
<td>IX</td>
<td>COL9A1, A2, A3</td>
<td>Short chain</td>
<td>Cartilage specific hyaline cartilage, vitreous humor</td>
<td>Multiple epiphyseal dysplasia, Stickler syndrome</td>
</tr>
<tr>
<td>X</td>
<td>COL10A1</td>
<td>Short chain</td>
<td>Cartilage specific growth plate (hypertrophic cartilage)</td>
<td>Schmidt’s metaphyseal dysplasia</td>
</tr>
<tr>
<td>XI</td>
<td>COL11A1, A2</td>
<td>Fibrils</td>
<td>Hyaline cartilage</td>
<td>Collagenopathy, types II and XI, Stickler syndrome</td>
</tr>
<tr>
<td>XII</td>
<td>COL12A1</td>
<td>?</td>
<td>Embryonic skin and tendon, periodontal ligament</td>
<td>?</td>
</tr>
<tr>
<td>XIII</td>
<td>COL13A1</td>
<td>Short chain</td>
<td>Endothelial cells, fibroblast, blood vessels</td>
<td>?</td>
</tr>
<tr>
<td>XIV</td>
<td>COL14A1</td>
<td>Glycoprotein</td>
<td>Fetal skin and tendon</td>
<td>?</td>
</tr>
<tr>
<td>XV</td>
<td>COL15A1</td>
<td>Interrupted collagen</td>
<td>Embryonic organs</td>
<td>?</td>
</tr>
<tr>
<td>XVI</td>
<td>COL16A1</td>
<td>FACIT</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

(Continued)
The fiber-forming collagens are well suited to resist the effect of pulling, that is, tension; thus the matrix of tendons and ligaments is mainly type I collagen. However, the fiber-forming collagens do not resist bending or compression well, and because the matrices of both bone and cartilage are subjected to these latter types of forces, they contain stiffening substances. In bone, the stiffening substance takes the form of a microcrystalline analog of geologic hydroxyapatite: \( \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 \) (Fig. 1-8). (The crystals in mineralized bone are too small to be seen by light microscopy, being approximately only \( 2 \times 2 \times 25 \) nm in size, but they can be visualized by electron and atomic force microscopy.) The apatite crystals provide strength in compression, although, as would be expected, they are weak in bending and tension.

During development and aging, the relative mineral content of the bone increases, whereas the water content decreases. The perfection and size of the hydroxyapatite crystals in the bone also increases with age. (In addition to its mechanical functions the mineral also has a primary role to play in calcium homeostasis [see Chapter 8].)

In articular cartilage, the filler between the collagen fibers is composed of large, negatively charged macromolecules, the proteoglycans (PGs) (Fig. 1-9). These are a group of heterogenous molecules consisting of protein chains and attached carbohydrates that have a sticky gel-like quality. The major PG in cartilage is aggrecan, which contains a protein core that has a molecular weight (Mr) of approximately 215,000 and to which carbohydrate side chains (keratan and chondroitin sulfate) are attached. The aggrecan molecules interact with hyaluronan and this interaction is stabilized by link protein (Fig. 1-10). As many as 200 individual aggrecan molecules (subunits) bind to one hyaluronic acid chain (Mr \( 1-2 \times 10^6 \)) to form a giant aggregate (Mr \( 5 \times 10^7 \) to \( 5 \times 10^8 \)).

PGs are highly charged molecules, often attached to collagen fibrils, which bind water, and this water accounts for approximately 70% of the wet cartilage tissue mass (Fig. 1-11). PGs in solution can expand to 50% of their volume. However, within hydrated cartilage the expansion of the PGs is restricted by the collagen network to approximately 20% of the maximum possible. The swelling (hydrolic) pressure thus created within the cartilage resists applied compressive loads.

When cartilage is loaded, some water is extruded; removal of the load permits the imbibing into the tissue of more water, together with essential nutrients, until the swelling pressure of the PGs is again balanced by the resistance of the collagen network.

The aggrecan shows an age-related decrease in size and enrichment in keratan sulfate relative to chondroitin sulfate. Associated with these changes is cartilage dehydration.
In addition to aggrecan, cartilage contains smaller PGs that contain dermatan sulfate (e.g., biglycan, decorin, fibromodulin, lumican). These PGs are present in lower concentrations than aggrecan, they bind growth factors and thus play a role in tissue metabolism and may also have a role in preventing joint adhesions. In older individuals, they show increasing concentration, especially in the superficial layers.

Articular cartilage also contains other extracellular noncollagenous proteins. Anchorin is a protein on the surface of chondrocytes involved in binding of these cells to extracellular matrix components, possibly transmitting information on matrix loading to chondrocytes. Fibronectin, thrombomodulin, thrombospondin, cartilage oligomeric matrix protein, cartilage-associated protein are found in cartilage.
but their precise functions are not yet known. The possible arrangement of some of these components within the cartilage matrix is shown schematically in Figure 1-12.

The matrix components of the connective tissues are manufactured as well as regulated by cells that themselves occupy only a small volume of the tissues. Nevertheless, these cells, that is, fibroblasts (cells that produce fibrous tissue, including ligaments and tendons), osteoblasts (cells that produce bone), and chondroblasts (cells that
produce cartilage, are essential to the production and maintenance of a healthy matrix. Disturbances in cell function may lead to an alteration in the rate of matrix synthesis or to the production of abnormal matrix constituents, as well as to altered breakdown. The breakdown of matrix constituents, either as a result of normal turnover or disease, occurs through the action of enzymes that may be derived either from the connective tissue cells themselves, from synoviocytes, or from blood-borne inflammatory cells.

**Bones**

**GROSS STRUCTURE AND FUNCTION**

Each bone has a limiting surface shell or cortex. Enclosed by the cortical shell are plates and rods of bone tissue variously known as spongy, cancellous, or trabecular bone (Figs. 1-13 and 1-14).

**Figure 1-11** Electron microscopic examination of cartilage demonstrates amorphous electron-dense deposits of proteoglycan between and attached to collagen fibers (× 102,900).

**Figure 1-12** Schematic illustration of the possible arrangement of collagen matrix constituents in hyaline cartilage.

**Figure 1-13** A. Cleaned and macerated specimen of a lower femur demonstrates both the decrease in cancellous bone and the thickening of the cortex as one approaches the diaphysis. B. Radiograph of the same specimen. Note the arrangement of the trabecular bone as well as the horizontal plate of bone that marks the site of the cartilage growth plate—the ‘epiphyseal scar.’
Cortical thickness varies considerably, both within a single bone and among different bones. For example, in normal adult vertebral bodies the cortex is very thin, whereas in the long bones, the cortex in the mid-diaphysis may reach more than a quarter inch in thickness. Even in a long bone, there is great variation in thickness between the ends of the bone (in which the cortex is thin) and the midshaft (in which the cortex is thick).

A moment’s reflection will make the reason for these differences obvious. The thick cortical bone is well suited to resist bending, and it is in the middle of the long bones that this force is maximal. In contrast, the cancellous bone is concentrated where compressive forces predominate, that is, in the vertebral bodies and expanded ends of long bones. Thus, the architecture of the bone reflects its function. This concept is summarized in Wolff’s law, which can be simply stated as: ‘Every change in the functional loading of a bone is followed by certain definite changes in internal architecture and external conformation’ (Fig. 1-15). As demonstrated in Figure 1-15D, a finite element analysis of the mathematical predictive strains acting on the proximal femur reveal a distribution similar to that seen in the imaging studies. It will be seen later that the microscopic arrangement of the constituents of the extracellular matrix, in the bone and all other connective tissues—for example, cartilage, tendon, meniscus, intervertebral disc—are no less precisely organized to fulfill their mechanical function.

**FIGURE 1-14** A. Close-up view of cancellous bone structure. B, Scanning electron micrograph (× 400). Note the packed collagen fibers of the matrix. C, Schematic representation of the perforated plates and the connecting rods of bone in the cancellous bone.
Bones are often compartmentalized by the morphologist into three indistinct zones: the epiphysis—the region between the articular end of the bone and the growth plate (or physis); the metaphysis—the region immediately below the growth plate (in the growing animal, the area of growth and most active modeling); and the diaphysis—the region between the metaphyses (i.e., the shaft of the long bones). Epiphysis, metaphysis, and diaphysis are useful descriptive terms, because many diseases predilect one or other of these compartments (Fig. 1-16).

**Periosteum**

Except at the musculotendinous insertions and at their articular ends, the bones are covered by a firmly attached thin but tough fibrous membrane, the periosteum. At the articular margins and tendinous insertions, the periosteum blends imperceptibly with the surface fibers of the articular cartilage, tendon, or ligament.

The periosteum is attached to the surface of the bone cortex by collagen fibers (the fibers of Sharpey). Where these fibers enter the bone, they are encrusted with mineral (hydroxyapatite), which cements them into the bone (Fig. 1-17). For this reason, any attempt at separation of the periosteum from the bone, especially in an adult, requires physical tearing of these fibers. (In children, the periosteum is only loosely attached to the underlying bone, whereas in adults, it is firmly attached. Thus the amount of post-traumatic periosteal reaction is much greater in children than in adults [Fig. 1-18].)
On microscopic examination, the periosteum is seen to have two layers: an outer fibrous layer and an inner cambium layer that has the potential to form bone (Fig. 1-19). In growing children, the cambium layer provides for the increasing diameter of the bone. In adults, the bone-forming potential of the periosteum is reactivated by trauma, infection, and growing tumors.

**Blood Supply**

The blood supply of the bone has been studied in cadaveric specimens by injection of latex or other substances into the arteries or veins, or both, and the results have been published in several atlases. These studies have shown that many capillaries enter the bone through the periosteum. This periosteal blood supply augments the principal nutrient arteries, which enter the medullary cavity by penetrating the cortex (usually at about the middle of the diaphysis), and the epiphyseal and metaphyseal vessels at the ends of the bone (Figs. 1-20 and 1-21).

The intraosseous veins are distinctly different from the arteries in being much more tortuous and having a significantly wider caliber.

**Figure 1-16** Bone compartments in the femur.

**Figure 1-17** The fibers of Sharpey are direct continuations of the periosteal collagen fibers around which the circumferential lamellae of the cortical bone have grown, thus firmly anchoring the periosteum.

**Figure 1-18** Photomicrograph of periosteal new bone in a child produced by the cambium layer of the periosteum following trauma (H&E, × 4 obj.). In a child, the periosteal new bone formation following trauma is abundant because of the weak attachment of the periosteum.
Bone matrix is synthesized by a layer of osteoblasts on the bone surface (Figs. 1-22 and 1-23). The osteoblasts are mesenchymal in origin and characterized by their abundant endoplasmic reticulum and their production of the enzyme alkaline phosphatase. The rate of matrix production at the time of biopsy can be approximated by the size of the osteoblasts. ‘Active’ osteoblasts are plump, whereas flat cells that line the bone surface can be considered quiescent or ‘inactive’ (Fig. 1-24). The point at which an ‘inactive’ cell becomes an ‘active’ cell is necessarily a subjective determination.

As the osteoblasts produce bone matrix and the matrix mineralizes, the osteoblasts become surrounded by the mineralized matrix, and are thus buried within the substance of the bone. This process, the osteoblasts become osteocytes (Figs. 1-25 and 1-26). (Because the spacing of the osteocytes is so obviously different from the closely packed osteoblasts on the surface, it is evident that not all osteoblasts on the surface are buried to become osteocytes. Some osteoblasts die via programmed cell death [apoptosis].)
The osteocytes are connected with each other and with osteoblasts on the surface of the bone by a series of cell processes that run through canals, the osteocytic canaliculi, permeating the bone tissue (Figs. 1-27 to 1-30). The syncytium of osteocytes that permeate the bone probably plays an important role in physiologic calcium homeostasis, and may also act as a sensing device to regulate skeletal mechanical homeostasis in accordance with Wolff’s law. (The osteocytic canaliculi do not cross the cement lines [see Fig. 1-39 for a description of cement lines].) Osteocytes produce different non-collagenous proteins than osteoblasts and can be distinguished by their production of dentin matrix protein 1 and sclerostin.

Associated with the osteoblasts that are actively forming bone matrix, a thin layer of nonmineralized bone matrix (osteoid), normally approximately 10 µm thick, separates the cellular layer from the underlying mineralized matrix (Fig. 1-31). The period between the deposition and subsequent mineralization of the organic matrix, the ‘mineralization lag time,’ has been estimated to be about 10 days. (The microscopic identification of nonmineralized bone matrix is a key factor in the diagnosis of certain metabolic disturbances of bone; however, its recognition depends on the preparation of undecalcified sections.)

On microscopic examination, the actively forming bone surfaces, as well as the inactive formed surfaces, are smooth. However, some bone surfaces have an irregular or ‘gnawed out’ appearance, and these surfaces either are actively resorbing or have been resorbed (Fig. 1-32). The cells responsible for resorption are the osteoclasts—large, multinucleated cells with abundant cytoplasm, which lie in cavities (Howship’s lacunae) on the bone surface (Figs. 1-33 and 1-34). (Although the osteoclast is usually a multinucleate cell, mononuclear forms of resorbing cells may also be seen.) Osteoclasts are derived from monocyte/macrophage precursors that are recruited to the bone microenvironment where locally produced cytokines
FIGURE 1-26 Transmission electron photomicrograph demonstrating portions of the cytoplasm of two active osteoblasts lying upon a mineralizing osteoid seam. Within the osteoid seam (lower left) is a newly formed osteocyte (× 10,000).

FIGURE 1-27 A. Photomicrograph to demonstrate the general disposition of the osteocytic canaliculi through which run the osteocytic processes. These processes join the osteocytes into a network that has attachments to the cells at the bone surface (H&E, × 10 obj.). B. High power of osteocytes at the surface (H&E, × 25 obj.).

FIGURE 1-28 Photomicrograph of osteocytes and osteocytic canaliculi seen by transmitted light in ground bone section (× 25 obj.).
Figure 1-29: Scanning electron photomicrograph demonstrating the osteocytes and their connecting canaliculi (× 750).

Figure 1-30: Electron photomicrograph of a portion of an osteocytic process in an osteocytic canaliculus in mineralized bone (× 50,000).

Figure 1-31: Photomicrograph of a section of undecalcified bone showing on the upper surface a prominent layer of active osteoblasts lying on an osteoid seam, with underlying mineralized bone. On the lower surface is an irregular resorbed surface, which in the left hand portion is filling in with new bone (von Kossa, × 25 obj.).

Figure 1-32: Photomicrograph showing active bone resorption in a tunneling pattern (H&E, × 10 obj.).

Figure 1-33: Photomicrograph showing an osteoclast in a Howship’s lacuna. Osteoclasts are identified by their abundant cytoplasm and multiple nuclei (Goldner stain, × 50 obj.).
and growth factors induce their differentiation into actively resorbing osteoclasts. Cells expressing the full morphologic and functional properties of mature osteoclasts are restricted to the immediate bone surface.

Electron microscopy reveals that the osteoclast has a ruffled border adjacent to the bone and contains many lysosomal bodies, mitochondria, and vesicular inclusions (Fig. 1-35).

Bone remodeling, the coordinated balance of bone formation and bone resorption, is regulated by systemic hormones (Table 1-2), blood-derived factors, and local mediators (Table 1-3). In addition to their direct effect on the skeletal tissue, hormones may also regulate the synthesis, as well as the effects, of the local mediators. An important mediator of osteoclastic resorption is nuclear factor kappa-B ligand. Its receptor (receptor activator of NF kappa-B or RANK) is expressed on the surface of osteoclasts and binding of RANK ligand to RANK results in osteoclast maturation and activation. Important local mediators of bone formation are the growth factors immobilized in the bone matrix, which are released by osteoclastic activity.

The established biochemical markers of bone turnover include serum alkaline phosphatase, serum osteocalcin (bone Gla protein), collagen N- and C-telopeptides, and the urinary excretion of calcium and collagen breakdown products, such as hydroxyproline or cross-linked collagen peptides. These cross-linked peptides are the most specific because they are only formed after synthesis is complete. Further discussion of the biochemical control of bone turnover is found in Chapter 7 and of calcification in Chapter 8.

### Table 1-2: Systemic Mediators in Cell Synthesis and Breakdown

<table>
<thead>
<tr>
<th>Systemic Mediators (Hormones)</th>
<th>Site of Action</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polypeptide Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>Osteoblast</td>
<td>Anabolic effect with ↑ rate of bone formation</td>
</tr>
<tr>
<td></td>
<td>Pre-osteoblast</td>
<td>Anabolic effect with ↑ rate of bone formation</td>
</tr>
<tr>
<td></td>
<td>Osteoclast (indirect)</td>
<td>Resorption via ↑ osteoclastic activity effected by secondary messenger</td>
</tr>
<tr>
<td>Calcitonin (CT)</td>
<td>Osteoclast</td>
<td>Inhibitory ↓ resorption</td>
</tr>
<tr>
<td>Insulin</td>
<td>Osteoblast</td>
<td>Stimulates matrix synthesis</td>
</tr>
<tr>
<td></td>
<td>Chondroblast</td>
<td>Stimulates matrix synthesis</td>
</tr>
<tr>
<td></td>
<td>Osteoclast</td>
<td>Regulates bone resorption</td>
</tr>
<tr>
<td>Growth hormone (GH)</td>
<td></td>
<td>May have an effect secondarily by stimulating the production of insulin-like growth factor by skeletal cells</td>
</tr>
<tr>
<td><strong>Steroid Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin-D3 [1,25(OH)₂D₃]</td>
<td>Osteoblast</td>
<td>Stimulates the synthesis of osteocalcin leads to ↑ bone resorption</td>
</tr>
<tr>
<td></td>
<td>Pre-osteoblast</td>
<td>Inhibits bone collagen synthesis</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td></td>
<td>Increased bone resorption, possibly indirect effect via ↑ PTH</td>
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<tr>
<td></td>
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<td>Decreased matrix synthesis</td>
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<tr>
<td>Sex steroids</td>
<td>Indirect action. Mediated by other hormones?</td>
<td>Important in skeletal maturation and in preventing bone loss during ageing process</td>
</tr>
<tr>
<td><strong>Thyroid Hormones</strong></td>
<td>Chondroblasts?</td>
<td>Necessary to normal growth and development, especially cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In adult ↑ thyroid causes increased bone resorption</td>
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</table>
**HISTOLOGY**

**Mature Bone**

In mature bone tissue the collagen fibers of the matrix are arranged in layers or leaves (hence the term 'lamellar bone'), and in each of these layers, the collagen bundles lie parallel to each other (Fig. 1-36). However, the orientation of the collagen bundles changes from one layer to the next, in a similar way to the layers in plywood (Fig. 1-37). In this manner, bone tissue gains much of its strength.

<table>
<thead>
<tr>
<th>Local Mediators</th>
<th>Site of Action</th>
<th>Mode of Action</th>
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</thead>
<tbody>
<tr>
<td><strong>Growth Factor Polypeptides Synthesized by Bone Cells</strong></td>
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</table>
| Insulin-like growth factor 1 (IGF-1) (somatomedin) | Pre-osteoblast  
Osteoblast | Increased cell replication  
Increased matrix synthesis | |
| Transforming growth factor β (TGFβ) | Pre-osteoblast  
Osteoblast | Increased cell replication  
Increased matrix synthesis | |
| Fibroblast growth factor (FGF) | Pre-osteoblast | Increased cell replication | |
| Platelet-derived growth factor (PDGF) | Pre-osteoblast | Bone cell replication and bone resorption | |
| **Blood Cell–Derived Factors** |                |                                         |
| Interleukin-1 (IL-1) | Pre-osteoblast  
Osteoblast | Stimulates bone cell replication. In low doses may also stimulate matrix production directly. Also stimulates bone resorption indirectly. | |
| Tumor necrosis factor (TNF) | Pre-osteoblast | Increased cell replication. Stimulates bone resorption, possibly indirectly. | |

**FIGURE 1-36** Segment of trabecular bone microscopically examined with polarized light (× 10 obj.). Although at first sight, the bone tissue appears as a seamless structure, it is made up of individual fragments that are joined at the cement lines.

**FIGURE 1-37** A, Diagrammatic representation of the layered (lamellar) appearance of bone shows how the alternating dark and light layers seen in Figure 1-36 are explained by the change in direction of the collagen fibers in each layer. B, Scanning electron photomicrograph demonstrating collagenous lamellae (layers) of the bone with the osteocytes between the lamellae (× 500).
In cortical bone, the layers are formed concentrically around a vascular core (haversian canal) to form an osteon (Fig. 1-38). On microscopic examination, it becomes apparent, in sections stained with hematoxylin and eosin, that surrounding each osteon and irregularly distributed throughout the trabecular bone there are distinct deep blue lines. These lines are the cement lines (Fig. 1-39). When histologic sections are examined microscopically using polarized light, a discontinuity of the collagen is seen on either side of the cement line. From these observations, it can be inferred that the bone is constructed of myriads of separate pieces like a three-dimensional jigsaw puzzle. (The size of these bone packets will affect bone strength because fracture propagation tends to occur along the cement lines. For this reason, the dense bone seen in Paget’s disease or osteopetrosis is paradoxically weaker than normal bone.)

Primary osteons are formed in the infant by the bony ingrowth of periosteal blood vessels, which follow a ‘cutting cone’ of osteoclasts that tunnel through the existing cortex. The tunnel thus formed then becomes partially filled in by layers of bone matrix, the most recently formed layer being that adjacent to the vessel. Subsequent secondary osteons are formed during the process of bone modeling by the outgrowth of vessels from existing haversian systems, each of which are preceded by a cluster of osteoclasts (Fig. 1-40).
Immature Bone

In addition to mature lamellar bone, another form of mineralized tissue exists in which the collagen matrix is irregularly arranged in a loose woven pattern resembling the warp and woof threads in a fabric (Figs. 1-41 and 1-42). The cells within this matrix are larger, more rounded, and closer together than those seen in lamellar bone. This type of mineralized tissue, which has been variously called woven bone, primitive bone, fiber bone, or immature bone, is seen during development, in fracture callus, in bone-forming tumors, and in conditions characterized by a highly accelerated rate of bone turnover (e.g., Paget’s disease and hyperparathyroidism). Its recognition by the pathologist is important because it usually indicates the presence of a disease process.

Marrow

The limited tissue space in the haversian canals of the cortical bone is occupied by fat and neurovascular tissue; in the much ampler tissue space of the cancellous bone in addition to fat and neurovascular tissue, there is often hematopoietic tissue. Hematopoietic tissue is found in all of the bones at birth, but with maturation, it becomes largely confined to the axial skeleton, that is, the skull, ribs, vertebral column, sternum, and pelvic girdle. The appearance of cellular marrow at other sites during adult life is abnormal and warrants investigation. In areas where hematopoietic tissue is normally present, the ratio of fat to hematopoietic tissue is about equal (Fig. 1-43). An increase or decrease in this ratio may indicate hematologic disease. (Interestingly, although in older individuals as well as certain disease states hyperplastic marrow may reappear in the long bones, it is often arrested at the site of the closed epiphyseal plate.)

GROSS STRUCTURE

The junction between adjacent bones is known as a joint. Of the three different types of joints, the most common is the diarthrodial joint, which is cavitated to form a freely movable connecting unit between two bones (Figs. 1-44 and 1-45). Hyaline cartilage (articular cartilage) covers the articulating surfaces of the diarthrodial joints; the exceptions are the sternoclavicular and temporomandibular joints, which are covered by fibrocartilage.
The function of a diarthrodial joint has three characteristics:

- The freedom of the articulating surfaces to move over each other
- The ability to maintain stability during use
- A proper distribution of stress through the tissues that comprise the joint so that they are not damaged.

These aspects of joint function depend upon:

- The shape of the articulating surfaces of the joint (Fig. 1-46)
- The integrity of the ligaments, muscles, and tendons that support the limb
- The cellular control of the mechanical properties of the matrices of the bone, cartilage, and the other tissues that together comprise the joint structure.

The second type of joint is the amphiarthrodial joint or symphysis, which is characterized by limited mobility, and exemplified by the intervertebral disc (Fig. 1-47) and symphysis pubis. The intervertebral disc is a fibrocartilaginous complex that forms the articulation between the vertebral bodies. It contributes to the mobility and stability of the spine as well as to the transmission of forces through the axial skeleton.
It should be noted that disc height is not the same in all segments of the spine; the cervical and thoracic discs are flatter than those of the lumbar region. Disc height also varies from front to back, relative to the curvature of the spine. With age, the disc becomes dehydrated and gets thinner.

The intervertebral disc can be divided into two components: an outermost fibrous ring (annulus fibrosus) and within a gelatinous core (nucleus pulposus). The annulus, if viewed from above, contains layers of fibrous tissue arranged in concentric circles. In each layer, the collagen fibers extend obliquely from vertebral body to vertebral body, with the fibers of one layer running in a direction opposite to that of the adjacent layer. The arrangement of the alternating layers provide for motion that is universal in direction, that is, flexion-extension-lateral bending and rotation (Figs. 1-48 and 1-49). The fibers of the annulus are attached by Sharpey’s fibers into the bony end-plates of the adjacent vertebral bodies (Fig. 1-50). The anterolateral component of the annulus, where the fibrous lamellae are stronger and more numerous, is almost twice the thickness of the posterior annulus. The nucleus pulposus typically occupies an eccentric position within the disc space, being closer to the posterior

![Figure 1-46](image_url)

**Figure 1-46** The shape of the joint determines (1) the freedom of the joint surfaces to articulate; (2) the stability of the joint; and (3) the distribution of stress on the tissues. **A**, Does not allow acceptable freedom of movement. **B**, Permits total freedom of movement but is unstable. **C**, Allows freedom of movement and is stable. However, the shape is not optimal because it is completely congruent and does not provide space between the articulating surfaces for lubrication or nutrition. When the joint is loaded, the stress is not equally distributed over the joint surfaces. **D**, Is the optimal shape for a joint because it is stable, it articulates easily, and there is some space between the joint surfaces so that the synovial fluid can move into the joint space to provide for the nutrition of the cartilage cells and the lubrication of the surfaces. This shape also distributes an increasing load equally, because the deformability of cartilage and bone enables the tissues to respond and conform to the stresses imposed on them.

![Figure 1-47](image_url)

**Figure 1-47** Intervertebral disc seen from above. Note the circumferential fibers in the annulus fibrosus. The nucleus pulposus (center) is rich in proteoglycan and water, and acts to resist compression. The circumferential fibers of the annulus prevent lateral displacement of the nucleus.

![Figure 1-48](image_url)

**Figure 1-48** Photograph showing frontal view of L5 with the adjacent intervertebral disc. Note the oblique disposition of the collagen fibers of the annulus fibrosus in this macerated specimen, which allows for universal movement between the vertebral bodies.

![Figure 1-49](image_url)

**Figure 1-49** Schematic drawing of the intervertebral disc demonstrates the layered arrangement of collagen fibers in the annulus. The fibers of each layer run at an approximately 30-degree angle to the surface of the vertebral body and in a direction opposite to that of the adjacent layer.
The tissue of the nucleus is separated from that of the bone of the adjacent vertebrae by a clearly defined layer of hyaline cartilage that extends to the inner margins of the insertion of the annulus (Fig. 1-51).

On microscopic examination, the nucleus pulposus shows chondrocytes as well as stellate and fusiform cells suspended in a loose myxoid fibrous matrix (Fig. 1-52).

Because no blood vessels are present in adult disc tissue, nutrients must reach the cells by diffusion from capillaries at the disc margins. The restricted flow of nutrients to the nucleus and inner annulus may contribute to disc degeneration in the adult.

The third and final type of joint is the fibrous synarthrosis, such as the skull sutures, which are nonmovable joints filled with dense collagenized fibrous tissue (Fig. 1-53).

**CARTILAGE**

The articular ends of the bones are covered by hyaline cartilage, which is a nerveless, bloodless, firm, and yet pliable tissue. Hyaline cartilage deforms under pressure but slowly recovers its original shape on removal of pressure (i.e., it has viscoelastic properties).

In young people, articular cartilage is translucent and bluish white; in older individuals, it is opaque and slightly yellowish (Fig. 1-54). This change with age in the appearance of articular cartilage is also seen in other connective tissues and is probably related to a number of factors, including dehydration of the tissues, increased numbers of cross linkages in the collagen, and the accumulation of lipofuscin pigment in the tissues (Fig. 1-55).

On microscopic examination, articular cartilage is characterized by its abundant glassy extracellular matrix with isolated, relatively sparse cells located in well-defined spaces (lacunae). It may be described as having four layers or zones: the superficial
(I), intermediate (II), deep (III), and calcified (IV). In the cell-rich superficial layer, zone I, the cells are relatively small and flat, oriented with their long axis parallel to the surface. In the intermediate zone II, the cells are larger and rounder, but also sparse and randomly distributed. In zone III or the deeper layer, the cells are even larger and have a tendency to form radial groups that apparently follow the pattern of collagen disposition in the extracellular matrix. In the calcified zone, that is, adjacent to the bone, the cells are mostly nonviable and the matrix heavily calcified (Figs. 1-56 and 1-57).

That some organized fibrous system exists within normal articular cartilage can be easily demonstrated by pricking the cartilage surface with a pin; this results in a split. If the pricking is repeated all over the surface, a constant pattern of split lines is revealed (Fig. 1-58). If the fissures reflect the internal fiber arrangement of the cartilage, then it can be inferred that on the surface, the fibers run parallel to the surface and in the general direction of the split line.

If the superficial layer of the cartilage is pared away and the exposed surface pricked, instead of a split only a small, round hole appears (Fig. 1-59). If the cut edge of the cartilage is pricked, a vertical split line is produced and this occurs in all planes of section (Fig. 1-60). These experiments indicate that in the deeper layers of the cartilage, the fibers are predominantly vertical (Fig. 1-61).
**FIGURE 1-56** A. The arrangement of adult articular cartilage. B. Photomicrograph of normal articular cartilage obtained from the femoral condyle of a middle-aged man (H&E, × 2.5 obj.).

**FIGURE 1-57** Electron photomicrographs to illustrate the typical appearance of chondrocytes at the surface, mid-zone, and deep-zone of the articular cartilage. 
A. At the surface, the cell is typically flattened and shows more cell processes on the inferior surface (× 10,000). B. In the mid-zone, the cell is round and demonstrates a well-developed endoplasmic reticulum and Golgi apparatus (× 10,000). C. The deep cells show vacuolization of the cytoplasm, with shrinking and irregularity of the nucleus (× 10,000).
Polarizing microscopy, transmission electron microscopy, and scanning electron microscopy confirm that the principal orientation of collagen in articular cartilage is vertical through most of its thickness and horizontal at the surface (Fig. 1-62).

Electron microscopic studies show that in the surface layer of articular cartilage the collagen fibers are closely packed, of fine diameter, and oriented parallel to the joint surface. The collagen content of cartilage progressively diminishes from the superficial to the deep layer and in deeper layers the collagen fibers are more widely separated, thicker in diameter, and vertically aligned in such a fashion as to form a web of arch-shaped structures. The collagen fibers of zones II and III are continuous with those in the calcified layer of cartilage but not with those of the underlying subchondral bone.

The very precise organization of collagen, as already described for the cartilage, bone, and annulus of the intervertebral disc, serves as a...
mechanical function. This must also be true for all connective tissues. For example, in the menisci of the knee, microscopic examination of carefully oriented sections has shown that the principal orientation of the collagen fibers is circumferential to withstand the circumferential tension developed during normal loading. The few small, radially disposed fibers probably act as ties to resist any longitudinal splitting of the menisci that might result from undue compression (Fig. 1-63).

The amount of PG in the cartilage matrix relates to the local mechanical requirements; it varies from joint to joint, and geographically within a single articular surface. The superficial layers of the cartilage contain much less PG than the deeper layers. In the deeper layers, there is a higher concentration of staining of the PGs with safranin O and methylene blue around the cells (the pericellular matrix) than between the cells (the intercellular matrix) (Fig. 1-64).

![Figure 1-63](image1)

**Figure 1-63** A, Photomicrograph of a section cut along the length of the meniscus in its mid-zone demonstrates that the collagen fibers run circumferentially (polarized light, × 1 obj.). B, Cross-section of the meniscus about halfway along its length demonstrates that most of the collagen fibers are cut crossways. However, especially on the tibial surface (lower) of the meniscus, the collagen fibers are cut lengthwise, indicating their radial disposition (polarized light, × 1 obj.). C, Diagrammatic representation of the distribution of collagen fibers in the meniscus of a knee. Collagen is oriented throughout the connective tissues in such a way as maximally to resist the forces brought to bear on these tissues. The majority of the fibers are circumferentially arranged; a few radially arranged fibers, particularly on the tibial surface, resist lateral spread of the meniscus. In the meniscus, tension is generated between the anterior and posterior attachments.

![Figure 1-64](image2)

**Figure 1-64** Portion of cartilage stained by methylene blue shows intense metachromasia around the chondrocytes in the deep part of the noncalcified cartilage. This represents staining of the proteoglycan. There is much less staining in the interterritorial matrix than around the cell. Even less staining is seen in the calcified cartilage (bottom) (× 25 obj.).
In histologic sections stained with hematoxylin-eosin, the junction between the calcified cartilage and the noncalcified cartilage is marked by a basophilic line known as the tidemark or calcification front, which is described in more detail in Chapter 10. This basophilic line clearly visible in the adult is not seen during development (Figs. 1-65 and 1-66).

Mechanical failure in the articular cartilage rarely, if ever, gives rise to the separation of bone and cartilage. However, when failure occurs, it is seen as a horizontal cleft at the junction of the calcified and noncalcified cartilage (at the tidemark) (Figs. 1-67 and 1-68).

Presumably, shear failure occurs at the tidemark due to the considerable change in the rigidity of the cartilage at this junction.

At their insertions, ligaments and tendons are also calcified, and just as the calcified cartilage layer is keyed into the irregular surface of the underlying bone (Fig. 1-69), so are the calcified insertions of ligaments (Fig. 1-70).

In addition to hyaline cartilage of which articular cartilage is composed, two other forms of tissue incorporating the term ‘cartilage’ have been described histologically. Fibrocartilage is a tissue in which the matrix contains a high proportion of collagen, but the cells are rounded with a halo of PG around them. It is found at the insertions of ligaments and tendons into the bone (Fig. 1-71), and on the inner side of tendons as they angle around pulleys, for example, at the malleoli. Fibrocartilaginous metaplasia is present in injured meniscus...
and other injured fibrous connective tissues, perhaps because the tissue is focally subjected to more compressive forces following injury. The second type of nonhyaline cartilage, elastic cartilage, contains a high proportion of elastic fibers in the matrix. It is present in the ligamentum flavum, external ear, and epiglottis (Fig. 1-72), where some element of stretch is necessary in the tissue (normal collagen lengthens only very slightly, even under heavy loads).

Both fibrocartilage and elastic cartilage incorporate the term ‘cartilage’ probably because the cells are rounded and lie in lacunae, and staining will reveal some PG staining in the pericellular areas, which gives them a superficial resemblance to the cells of hyaline cartilage. However, the mechanical functions of these tissues are very different from those of hyaline cartilage. Both fibrocartilage and elastic cartilage function principally as resisters of tension, with, however, some focal element of compression. On the other hand, hyaline cartilage is mainly subject to and resists compressive forces.

SYNOVIAL MEMBRANE

The synovial membrane lines the inner surface of the joint capsule and all other intra-articular structures, with the exception of articular cartilage and the meniscus; it consists of two components. The first is the synovial lining (or intimal layer) bounding the joint space; this is predominantly cellular. The second component is a supportive, or backing layer, formed of fibrous and adipose tissues in variable proportions.

The surface of the synovial lining is smooth, moist, and glistening, with a few small villi and fringe-like folds (Fig. 1-73). The cellular elements of the joint lining consist of a single row or sometimes multiple rows of closely packed intimal cells with large elliptical nuclei (synoviocytes); in the subintima are other connective tissue cells, including fat cells, fibroblasts, histiocytes, and mast cells (which are omnipresent in connective tissue) (Figs. 1-74 and 1-75).
FIGURE 1-71 Photomicrograph of a tendon insertion. Note that at the insertion, the cells of the tendon are rounded and lie in lacunae. This is described as fibrocartilaginous metaplasia. Elsewhere in a tendon the fibrocytes are flattened (H&E, × 10 obj.).

FIGURE 1-72 Photomicrograph of ear cartilage. Although the cells resemble those seen in hyaline cartilage, the matrix contains many elastic fibers. These fibers appear red in this section stained with phloxine and tartrazine (× 25 obj.).

FIGURE 1-73 Photomicrograph of synovium showing the simple lining and the fibroadipose subsynovial tissue (H&E, × 4 obj.).

FIGURE 1-74 Photomicrograph of synovium showing a delicate synovial lining resting on a fibroadipose subintimal layer which is rich in capillaries, lymphatics, and nerve endings (H&E, × 25 obj.).
Electron microscopic studies have revealed two principal types of synovial lining cells, which have been designated by Barland as types A and B. (Many cells have features of both types and have been called intermediate.) The less common cell (type A) has many of the features of a macrophage, and there is good evidence that it is structurally adapted for phagocytic functions (Fig. 1-76). The more common type B cells are richly endowed with rough endoplasmic reticulum, contain Golgi systems, and often show pinocytic vesicles (Fig. 1-77). Normal synovial intima contains 25% of type A and 75% of type B cells.

The synovial membrane has three principal functions: secretion of synovial fluid hyaluronate (B cells); phagocytosis of waste material derived from the various components of the joint (A cells); and regulation of the movement of solutes, electrolytes, and proteins from the capillaries into the synovial fluid. Thus the synovium provides the metabolic requirement of the joint chondrocytes and a regulatory mechanism for maintenance of the matrix.

In addition to lining the joints, synovial membrane lines the subcutaneous and subcutaneous bursal sacs, which permit freedom of movement over a limited range, for the structures adjacent to the bursae. Synovial membrane also lines the sheaths that form around tendons wherever they pass under ligamentous bands or through osseofibrous tunnels.

**Bone Growth and Development**

Unlike most tissues, mature bone tissue grows only by deposition on the surface of an already existing calcified substrate. As John Hunter put it, 'Bones do not grow by fresh matter being put into all parts, so as to push the old matter to a greater distance but by new matter laid upon the external surface.' In contrast to bone, cartilage grows by interstitial cellular proliferation and matrix formation.

With the exception of the cranial vault and a few other bones, most of the embryonic skeleton is first formed of cartilage, and cartilage proliferation plays an important role in continuing skeletal growth and modelling.

Before any bone formation occurs within the embryonic cartilage skeleton, the chondrocytes toward the middle of the individual skeletal parts become larger and more separated by interstitial matrix (Fig. 1-78). As the cells in the center of the shaft of a long bone continue to enlarge, the cartilage matrix lying between the cells becomes calcified, and the cells die (Fig. 1-79).

Although the mechanisms of calcification are not completely understood, it is clear that the regulation of cartilage calcification is essential to bone growth and modeling. The hypertrophic chondrocytes adjacent to the calcification front show electron microscopic alterations in their cytoplasmic structure and have been found to synthesize collagen type X, which appears to be

![Synovial fluid](image1)

**FIGURE 1-75** Schematic of the synovial membrane showing the typical arrangement of cells. The transudation of the synovial fluid requires specialized capillaries such as those that are seen in the renal glomeruli.

![Electron micrograph of an A cell](image2)

**FIGURE 1-76** Electron micrograph of an A cell shows abundant mitochondria and dense inclusion bodies (x 10,000).
an important mediator of vascular invasion. Still other factors provide sites for initial hydroxyapatite deposition, enzymes that increase local calcium and phosphate concentration, and enzymes that degrade mineralization inhibitors or cause the formation of mineralization promotors.
FIGURE 1-80 Photomicrograph of a section through a metacarpal from a 7-week fetus. In the diaphysis the cartilage matrix stains a deeper blue, indicating that it is calcified. Around the calcified cartilage matrix is a narrow cuff of immature bone (Trichrome stain, × 4 obj.).

FIGURE 1-81 A. Photomicrograph of a long bone removed from a 10-week fetus (Trichrome, × 4 obj.). B. Close-up shows the calcified cartilage (right) and the diaphyseal bone cuff (left) covered by condensed mesenchymal tissue that forms the periosteum. Penetrating through the bone cuff into the calcified cartilage is a blood vessel. This blood vessel will eventually erode through the calcified cartilage entirely, bringing in osteoblasts to form the earliest primary spongiosa (Trichrome, × 16 obj.).
seen to line up on the surface of the remaining calcified cartilage and deposit a bony matrix. This process of cartilage calcification, vascular invasion, and deposition of bony matrix on the remaining calcified cartilage is known as endochondral ossification. It is the process by which cartilage is transformed into bone.

The bone first laid down, that is, with a core of calcified cartilage and primitive bone on the surface, is commonly known as the primary spongiosa (Fig. 1-82; see also Fig. 1-94). As the primary spongiosa is remodeled and the calcified cartilage removed, the bone trabeculae come to be formed entirely of bone tissue (referred to as secondary spongiosa).

In the fetus, the process of endochondral ossification continues until a considerable portion of the shaft of a long bone has been converted into osseous tissue and only the ends of the bone are still formed of cartilage (Fig. 1-83). Throughout this process, the cartilage at the bone ends is continuously proliferating and enlarging by interstitial growth. As the cartilage cells in the epiphyseal bone ends approach the midshaft of the bone, they undergo enlargement and degeneration; subsequently the cartilage matrix calcifies, and eventually vascular invasion and the formation of more primary spongiosa occur; this zone of metamorphosis is referred to as the physis or growth plate and, in this way, the bone continuously grows in length (Figs. 1-84 and 1-85).

During the early stages of skeletal development, the locations of joints are marked by a condensation of mesenchymal cells. Only after the fifth to eighth week of intrauterine life do these cells undergo flattening and apoptosis to form a joint cleft (Figs. 1-86 to 1-88).

At some point during the growth period, usually during infancy and childhood, a secondary center of ossification is formed within the cartilaginous end of the bone (Figs. 1-89 and 1-90). Calcification occurs initially at the middle of the secondary center. This area is then invaded by blood vessels carried through canals, that develop from invagination of the delicate surface perichondral covering of the epiphysis and the process of endochondral ossification ensues (Fig. 1-91). As the secondary center of ossification grows, the only remaining cartilage is that which covers the articular end of the bone (articular cartilage) (Fig. 1-92) and a thin layer or plate of cartilage lying between the secondary center of ossification and the main part of the bone shaft (the growth plate or physis) (Figs. 1-93 to 1-96).

The cartilage of the growth plates continues to proliferate and undergo endochondral ossification until growth slows during adolescence. At cessation of growth, the epiphyseal plate is perforated by blood vessels and becomes obliterated (Fig. 1-97). However, the position of the growth plate in the form of a bone plate is seen on radiologic examination and in anatomic specimens throughout life (Fig. 1-98).

During the growth period, acute illness may lead to a temporary cessation of growth, and the stigma of this cessation may remain for many years in the shaft of a bone as a linear density seen on radiographic images, paralleling the epiphyseal scar and known as a Harris line or growth arrest line (Fig. 1-99).

The bones of the skull, as well as some of the facial bones and most of the clavicle, form from undifferentiated connective tissue cells (mesenchyme) in the same manner as the initial periosteal bone cuff, that is, without a pre-existing cartilage model. These bones are termed membranous bones, and they grow only by the apposition of new bone on the surface. Membranous bones have no cartilaginous growth plates (Figs. 1-100 to 1-102).
FIGURE 1-84 Photomicrograph of the upper end of the femur showing the junction between the newly formed bone and the epiphyseal cartilage. The bone grows in length by the process of endochondral ossification, in which the calcified cartilage is invaded by blood vessels from the metaphysis and replaced by bone (H&E, × 10 obj.).

FIGURE 1-85 A. Photomicrograph to show the zone where bony growth occurs. This is called the physis, and vascular invasion from the metaphysis results in the replacement of cartilage with bone during the growth process. Note that the periosteal bone extends beyond the growth plate, thereby mechanically stabilizing this zone. (This area is shown in higher power in B. Abnormalities in this zone may explain the development of osteochondromas. See Chapter 17.)
Figure 1-86 Photomicrograph of a sagittal section through the fetal knee joint at the sixth week of gestation, showing the condensation of mesenchymal cells marking the future joint space (H&E, × 10 obj.).

Figure 1-87 Photomicrograph of a sagittal section through the knee joint at the ninth week of gestation, showing the development of the joint space from the periphery towards the center of the joint (H&E, × 10 obj.).

Figure 1-88 Photomicrograph of a section through the hip joint at the 10th week of gestation, showing a fully developed joint space (H&E, × 4 obj.).

Figure 1-89 The secondary center of ossification is demonstrated in the lower end of the femur. This area increases in size by the process of maturation and calcification of the cartilage around the secondary center, with subsequent endochondral ossification (H&E, × 1 obj.).
**FIGURE 1-90** A, Schematic diagram indicating the times of ossification of the skeleton. B, In this total body bone scan the forming epiphyses are clearly identified by the intensity of isotope uptake.

**FIGURE 1-91** The vessels that feed the ossification center of the epiphysis are carried in canals through the epiphyseal cartilage; one of these canals is demonstrated here (H&E, × 25 obj.).

**FIGURE 1-92** Photomicrograph of articular cartilage from a child. Vascular ingrowth from the deep articular cartilage is associated with bone formation. Pericellular calcification is present around the deep chondrocytes; however, the tidemark is as yet only rudimentary (H&E, × 4 obj.).

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<td>11-12 y</td>
<td>16-17 y</td>
<td></td>
</tr>
<tr>
<td>6 m</td>
<td>17-18 y</td>
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<tr>
<td>9-12 y</td>
<td>17-18 y</td>
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y = Years  
m = Months  
fm = Fetal months
FIGURE 1-93 Photomicrographs of similar sections through the growth plate stained by three different stains and demonstrating the appearance of the growth plate during active bone growth. At the top of the field is a portion of the epiphysis, and the cartilage cells in the growth plate which are closest to this region are proliferating cells. Further down, the cells begin to palisade into vertical columns, and as they approach the metaphysis the cells hypertrophy and the matrix calcifies. The calcified matrix is invaded by blood vessels and bone forms on the residual calcified cores of cartilage (A, H&E; B, Safranin O to show the distribution of PG; C, von Kossa to show the distribution of calcium; all × 4 obj.).

FIGURE 1-94 Diagram of the growth plate.
FIGURE 1-95 Specimen of the upper end of the tibia in an immature pig. The vessels have been injected with barium sulfate and the bone decalcified. The ramifying vessels in the metaphysis, which provide for endochondral ossification, are clearly seen.

FIGURE 1-96 A bisected traumatically avulsed femoral head from an 8-year-old child. The photograph shows first the cup-shaped metaphyseal surface of the growth plate and secondly its knob-like protuberances, both of these structural features help stabilize the epiphysis and prevent slippage during the growth period.

FIGURE 1-97 A. A gross photograph of the distal femur of a 17-year-old boy shows the residual growth plate, more intact (right) toward the bone margin. (B) Photomicrograph of a portion of the more intact growth plate. Note the inactive metaphyseal surface (lower) (H&E, x 10 obj.). (C) In another area the growth plate is still open on the left side of the field; however, on the right side, bony continuity has been established between the metaphysis and the epiphysis. At this point, growth can be said to have ceased. In general, the plate first closes in its central portion, whereas the peripheral portion of the plate is the last part to close (H&E, x 4 obj.).
**FIGURE 1-98** Radiograph of the ankle in an adult shows the epiphyseal scar in the lower end of the tibia.

**FIGURE 1-99** Radiograph of the tibia in a child with an open epiphyseal plate. In the shaft of the tibia a number of radiopaque lines (Harris line) are clearly visible, representing episodes of growth arrest.

**FIGURE 1-100** Photomicrograph of a section taken through the skull area of an 11-week fetus. The bone presents first as cell condensations that secrete an extracellular matrix of immature bone (H&E, × 16 obj.). Two islands of bone matrix are clearly seen in the upper third of the section.

**FIGURE 1-101** Drawing of a macerated specimen of the parietal bone obtained from an approximately 20-week fetus demonstrates how individual foci of secreted bone matrix fuse together initially to form a network of bone; later this network will develop into a plate.
FIGURE 1-102 Photomicrograph of a section of calvarial bone from a 19-week fetus. The dural surface is on the lower border of the field, and the epidermal surface is on the upper border. Note the resorptive activity along the dural surface and the blastic activity along the epidermal surface, which allows for expansion of the cranium (H&E, × 4 obj.).
This compound microscope has a Wenham binocular body tube c. 1870 that is unsigned but similar to microscopes manufactured by J. Swift, London. The eyepieces in the picture are signed by Henry Crouch, and appear in a catalog dated 1866 [authors collection].
A complete understanding of the patients’ pathology and the selection of the best material for histologic examination depends on adequate communication between the clinician, the radiologist, and the pathologist. Regrettably, more often than not this does not occur even in the best institutions. For the general reader to better understand the limitations of tissue pathology, some of the more important aspects of technique are dealt with in this chapter.

**Gross Examination**

Bone specimens received by the surgical pathologist often consist only of fragments, and the anatomy may be unrecognizable. When it is important to the diagnosis and subsequent management of the patient for the fragments to be differentiated, it is the surgeon’s responsibility to ensure that the individual pieces are separately submitted and correctly labeled.

When a larger piece of bone is submitted for examination, anatomic landmarks should be carefully sought, and if a photographic record is desirable, careful dissection of the soft tissue adherent to the bone surface is essential. Photographs without this step are likely to be less informative and visually disappointing (Fig. 2-1).

Cutting the specimen into thin slices (3 to 5 mm) allows both visualization of the interior of the bone and proper fixation of the tissue. Large specimens can be cut on a band saw, and smaller specimens on a small circular saw (Fig. 2-2). After using the saw, it is important to gently wash the cut surface of the bone tissue under running water. This ensures that any fragments of bone dust and other tissue debris generated by the sawing are washed out of the interstices of the marrow space. Unless this is done, microscopic artifacts may appear on the histologic sections (see Fig. 2-25).

Visual examination of the cut surface is particularly helpful with tumors where it may be possible first to assess the viability of the tumor and, in some cases, to make a preliminary differential diagnosis based on the consistency and type of matrix production (Fig. 2-3). A dissecting microscope mounted directly over the grossing area in the surgical pathology laboratory is useful for better visualization of the morbid anatomy and for correlating the gross appearance of a tissue with the microscopic histology (Fig. 2-4). Bone necrosis is readily recognized because of its opaque, yellow appearance in contrast to the translucent appearance of living bone tissue (Fig. 2-5).

**Radiographic Examination of Bone Specimens**

The pathologist should assess the texture and the porosity of the bone, and whether increased or decreased from normal. Although this is often done at autopsy by a prosector who presses on the cancellous bone with his or her thumb, porosity and texture are much better assessed radiographically and a valuable adjunct to the examination of bone specimens is the preparation of radiographs using low-voltage x-rays (Faxitron X-Ray; Wheeling, IL) (Fig. 2-6). The detail revealed by such films depends on the thickness of the specimen: the thinner the slice, the more detail will be revealed (Fig. 2-7). The radiograph is particularly useful for assessing alterations in bone texture and organization (Fig. 2-8). Fine-grain radiographs can also be helpful intraoperatively in lieu of a frozen section in finding the nidus of an osteoid osteoma (Fig. 2-9). In some cases, the radiograph may be a useful guide in deciding which portions of the tissue to submit for microscopic examination (Fig. 2-10).

**Specimen Photography**

Color images are useful both for research and for teaching purposes. In either case, as mentioned earlier, before taking a photograph or obtaining a digital image the specimen should be adequately washed so that both the bone and the lesion are readily differentiated and dried so that there are no abnormal highlights from reflections of the flood lamps. The specimen should be aligned according to anatomic principles, and where appropriate a scale should also be included in the image (Fig. 2-11). (Because of the instant availability of the image, digital photography has made the process much easier [Fig. 2-12].)
White light has a broad wavelength range, which results in variable penetration of light into a translucent object, thereby precluding a sharp focus of the surface. This problem can be largely overcome by the use of short-wave monochromatic light. We have found a black (ultraviolet [UV]) light source to be inexpensive and to provide very satisfactory photographs of surface texture (Fig. 2-13).

FIGURE 2-2  A, A band saw is used to cut large specimens. Note that soft tissue left attached to the bone is liable to catch in the saw blade and be torn. B, Small pieces of bone can be cut on a circular saw, such as shown here, using a diamond blade and a micrometer screw to advance the specimen.

FIGURE 2-3  This patient had a large tumor projecting from the scapula surface. The glassy blue-white appearance is most consistent with a tumor of cartilaginous origin.

Microscopic Examination

PREPARATION OF TISSUE FOR MICROSCOPIC EXAMINATION

Preparation of tissue sections containing the maximum information depends on choice of the right piece of tissue and on proper processing of the tissue blocks.

To ensure adequate penetration of the processing fluids, the submitted tissues should not exceed 3 to 4 mm in thickness. It is important to use an adequate amount of fresh solution for fixation, because the fixative is being used up in the process. Far too
frequently, specimens from the operating room are received barely covered by fixative, and irreversible tissue breakdown may have taken place as a result of inadequate fixation.

In general, the volume of fixative should be at least 10 times the volume of the tissue. For most purposes, formalin provides adequate fixation. However, the formalin should be buffered to prevent the formation of formalin pigment, which can interfere with the proper interpretation of other pigments that may be present, such as iron. Buffering the formalin also prevents the formation of formic acid, which might otherwise result in undesirable decalcification. It is worth noting that optimal fixation with formalin is probably achieved in less than 12 hours.

If decalcification is desired after adequate fixation of the tissue, 5% nitric acid will produce decalcification in a reasonable time with good preservation of the tissue. However, an adequate volume of acid should be used, approximately 10 to 20 times that of the tissue. Because the acid is neutralized as the calcium is removed from the bone, it should be changed frequently; in our laboratory, we change the acid twice a day. To ensure access of the acid to the tissue, gentle agitation using a shaker is a helpful procedure (Fig. 2-14). (The adequacy of decalcification can be assessed by preparing radiographs of the specimens, which can be done with the tissues in their cassettes [Fig. 2-15].)

After decalcification has been achieved, it is essential to wash the tissue in running water for at least 12 hours, to ensure good...
differentiation of the hematoxylin-eosin (H&E) stain. If the bone tissue is overly decalcified, or if the acid is inadequately removed, poor staining will result.

The preparation of histologic sections of bones for routine microscopic examination has, in general, required the removal of the inorganic mineral component by acidic solutions, as just described. For this reason, the quantity and quality of mineralization have been impossible to assess. The technique of embedding bone in methyl methacrylate, although very time consuming, not only allows thin histologic sections of bone to be cut without prior decalcification but also has the considerable advantage of achieving a better preservation of tissue relationships. (Because of the tough collagenous nature of the organic matrix, such preservation is often difficult to obtain when routine paraffin embedding is used [Fig. 2-16].)

Bone can be prepared for electron microscopy by fixing diced tissue in paraformaldehyde or in glutaraldehyde. The tissue can be decalcified using ethylene diamine tetra-acetic acid (EDTA), or the calcified tissue can be sectioned with a diamond knife.

STAINS

For most purposes, a routine H&E-stained section is adequate. However, a variety of staining techniques may be used to demonstrate the different components of the matrix. Collagen can

FIGURE 2-8 Radiographs to demonstrate the relative radiolucency of osteoporosis (A) and density of metastatic cancer (C). The normal bone (B) has readily identifiable vertical and horizontal bone trabeculae.

FIGURE 2-9 Thirteen fragments of bone were submitted from a patient with an osteoid osteoma. Fragment 6 (A) shows a portion of the nidus, recognizable by the dense, finely packed area of bone. Fragment 13 (B) is entirely cancellous bone. Another example of an osteoid osteoma in situ is shown in C. Note the band of relative lysis around the nidus of the osteoid osteoma.
be demonstrated by a trichrome stain or by the van Gieson stain
(Fig. 2-17). (However, perhaps the most useful technique for exam-
ing collagen is polarized light microscopy [see Fig. 2-24C].) The
proteoglycans (PGs) can be demonstrated by the safranin O stain,
alcian blue stain, and less specifically by toluidine blue (Fig. 2-18).
Mineral components can be demonstrated only in undemineralized

**FIGURE 2-10** Radiograph of the distal end of a fibula resected because of
an intraosseous tumor that proved to be a chondrosarcoma. The margins
of the tumor are clearly seen on the radiograph, which therefore is an excellent
guide to mapping of the section; also seen are the characteristic rings of
calcification in the tumor.

**FIGURE 2-11** A. This photograph shows a
number of photographic errors, including a
dirty background, slight lack of focus on the
front of the patella, highlights caused by an
improperly dried specimen, poor positioning,
poor lighting, and no scale for identification.
B. A more correctly taken photograph of the
same specimen for comparison.

**FIGURE 2-12** Illustration of the set-up used in our laboratory for digital
photography.

**FIGURE 2-13** The articular surface of a patella with early degenerative
disease illuminated with black (ultraviolet) light.
tissue, and the mineral can be stained by two techniques: alizarin red, which stains the calcium components of the hydroxyapatite red, and the von Kossa method, which stains the phosphate component as well as other calcium salts (e.g., carbonate and oxalate) black (Fig. 2-19). (The distribution of mineral in the tissue can also be studied by microradiography, using low-kilovoltage x-rays from an x-ray tube with a fine focal spot. These radiographs are prepared using thin slices of bone cut with a diamond saw at approximately 100 µm [Fig. 2-20].)

Osteoblasts and osteoclasts can be stained using alkaline phosphatase and tartrate-resistant acid phosphatase stains, respectively. These stains can be carried out on unfixed frozen sections or on glycol methacrylate sections prepared after brief fixation.

**Immunohistochemistry**

No procedure has revolutionized diagnostic histopathology as much as has the introduction of immunohistochemical staining. The technique is generally sensitive and specific, and most importantly, can be applied to routinely processed paraffin blocks (even after many years).

As with any technique, there are pitfalls, including cross-reactivity, technical failures (including the failure to include proper positive and negative controls), and perhaps most importantly, the failure to correlate the results with the H&E sections and the clinical findings.

The objective in immunohistochemistry is a more precise characterization of the protein constituents of cells and matrix and the identification of the cell line of origin in undifferentiated or poorly differentiated tumors (Fig. 2-21).

The concentration of antigen in tumor cells may predict the aggressiveness of the tumor or, as in the case of estrogen receptor in breast cancer, the prognosis.

The most commonly used antibody markers are

1. Those that distinguish the five major groups of intracytoplasmic intermediate filaments including vimentin (mesenchymal cells), cytokeratin (epithelial cells), desmin (muscle), glial fibrillary acidic protein (glial cells), and neurofilament protein (most neuronal cells).
2. Specific epithelial markers—epithelial membrane antigen.
3. Muscle markers—in addition to desmin, actin, smooth muscle actin.
Section I: Normal

5. Neural markers—includes S-100 protein (schwannian, synaptophysin).

6. Specific markers for lymphomas and small cell tumors.

Antibodies prepared against various collagen types and against constituents of PG aggregates have been used as investigative tools to study the distribution of the matrix constituents (Fig. 2-22).

A number of useful websites are now available for information on both immunohistochemistry and cytogenetics.

Genetic Markers

The majority of neoplastic tumors, both benign and malignant, are characterized by cytogenetic abnormalities. These abnormalities are believed to be the result of sequential genetic alterations in normal progenitor cells, which, in turn, lead to a clonal expansion of phenotypically transformed cells.

Normal human cells contain 22 pairs of autosomal chromosomes and two sex chromosomes. Each chromosome has a long arm (q) and a short arm (p), and is characterized by alternating dark and light bands that can be stained using either Giemsa stain or a fluorescent stain (Quinacrine).

The transformed cells of a neoplastic tumor often contain multiple clonal genetic abnormalities, some of which, like deletions of large chromosomal segments, trisomy, or chromosome translocations, are visible in chromosome preparations. [In the description of translocation t(11;22)(q24;q12), t indicates a reciprocal exchange of material between two different chromosomal arms. The first set of parentheses contain the chromosomes involved and the second set the break points and arms of the chromosomes involved]. Other mutations such as substitution or deletions of individual DNA nucleotides cannot be detected optically in cytogenetic preparations.

Cytogenetics requires fresh viable tissue that must be transported, cultured, and maintained in a sterile state, all of which is difficult as a routine, laboratory test. However, if a segment of DNA corresponding to a specific gene can be prepared and labeled, then it can become a probe for the gene in question. Most molecular cytogenetic methods in present use are based on in situ

Figure 2-16 A. Photomicrograph of a section of bone marrow decalcified and embedded in paraffin. B. Photomicrograph of a section of bone marrow undecalcified and embedded in methyl methacrylate. Note that this is a thinner section than that demonstrated in A and therefore has more cytologic detail without obscuring overlay (both views, H&E, x 10 obj.).

Figure 2-17 A. Photomicrograph of a portion of developing cartilage, tendon, and vascularized adipose tissue stained by Masson’s trichrome stain. Muscle stains red, as seen in the media of the artery in the lower left, and collagen stains blue. B. The same tissue stained with Verhoeff’s elastic stain (van Gieson as counterstain), in which the collagen stains red and the elastic tissue black. The muscle fibers stain yellow-green (x 4 obj.).
hybridization using fluorescein as a label. Cocktails of probes that can target an entire chromosome are useful for demonstrating chromosomal translocations and deletions. A number of “break-apart” probes designed for diagnosis of translocation-associated sarcomas are now available commercially. These probes span the breakpoint of one gene involved in a translocation and result in two fluorescent signals when the gene has been broken apart by such a rearrangement.

Genetic studies have proved to be particularly valuable in the differential diagnosis of lymphoma, small round cell tumors such as

FIGURE 2-18 Photomicrograph of a portion of growth plate and underlying metaphysis. The PG in the matrix is stained red with safranin O (A) and blue with alciain blue (B). With toluidine blue (C), the cartilage is stained purple, that is, the color of the dye is changed from blue to purple, which is described as metachromasia (× 4 obj.).

FIGURE 2-19 A. Section of undecalcified bone stained with alizarin red, which stains the calcium salts red. The osteoid is counterstained with azure blue (alizarin red, × 10 obj.). B, Section of undecalcified bone stained by von Kossa’s method, in which the calcium salts are stained black. The osteoid is counterstained with acid fuchsin (von Kossa’s, × 10 obj.).
Ewing’s sarcoma, and some spindle cell tumors; for example, more than 90% of synovial sarcoma, both monophasic and biphasic, are characterized by a reciprocal translocation of chromosomes X and 18 t(X;18)(p11;q11).

**Fluorescence Labeling**

The autofluorescing antibiotics, known as the tetracyclines, have an affinity for the mineral at actively mineralizing surfaces. They serve well as supravital in vivo markers of mineralization because they are clearly visualized when a section is examined using UV light. Two labels, usually of different tetracyclines, must be used to determine both the extent and the rate of mineralization. The protocol for tetracycline labeling used in our laboratory is as follows: 250 mg of oral oxytetracycline are given four times a day for 3 days. After an interval of 12 days, demeclocycline, 300 mg four times a day, is given for another 3 days. The bone biopsy is then performed 4 to 7 days after the last dose of demeclocycline. The specimen is fixed...
in 70% alcohol, which helps to protect against leaching of both the label and mineral from the tissue. Unstained sections should be stored in the dark to prevent fading of the fluorescence before they are examined. At the time of examination, they should be covered with optically inactive oil for optimal visualization of the label. In our experience, 5 µm–thick sections are adequate for the visualization of properly applied labels. In a normal biopsy, both single and double labels may be observed, and these labels are usually sharp and distinct (Fig. 2-23). In case of certain metabolic disturbances, the labels have specific morphologic features that reflect the condition of the mineralizing bone–osteoid interface (see Chapter 8).

In addition to the commonly used transmitted light optical microscopy, a number of other microscopic techniques are particularly useful for examination of connective tissues. Differential interference contrast (or Nomarski optics) is especially valuable because it provides a pseudo–three-dimensional appearance to the tissue, which can be helpful in understanding the structure. In addition, this system gives some improvement of resolution, so that the resulting photographic images may be clearer than those obtained with transmitted light microscopy (Fig. 2-24A and B). Perhaps the most useful microscopic technique for the examination of connective tissues uses polarized light, not only because it clearly reveals the collagen fibers but also because it enables the determination of the orientation of the collagen and the study of the microarchitecture of the tissue (Fig. 2-24C). This information can be very helpful in the interpretation of disease states (e.g., in Paget’s disease) or in delineating reparative scars.
An important diagnostic procedure in the clinical diagnosis of crystal synovitis is the examination of synovial fluid for crystals (see Chapter 12 for a complete discussion of this procedure).

The most common and one of the most troublesome artifacts encountered in sections of bone is the presence in the marrow space of irregular fragments of basophilic material that may be mistaken for tumor or some other morbid condition (Fig. 2-25). These fragments represent bone dust and other debris that are driven into the interstices of bone during the slicing process. This artifact can be avoided by washing the surface after sawing and by cutting into the paraffin block a little way before taking sections for microscopic examination. A decidedly rare artifact may occur from the acid decalcification of the bone. Under certain conditions a secondary calcium salt crystal may be deposited in the tissue in the form of calcium brushite (Fig. 2-26).

Intraoperative frozen sections constitute an important tool in assisting a surgeon in his decision making. Whether for diagnosis or the evaluation of resection margins, the frozen section can help in determining the definitive surgical procedure for a particular case (Fig. 2-27).

With the increasing use of implant devices, it is especially important to differentiate between infection and a cellular reaction to implant debris when treating failed prostheses. In the case of suspected neoplasia, frozen sections can usually differentiate between tumor, inflammation, or necrotic tissue.

The pitfalls of frozen section are inadequate tissue, tissue that is not representative of the entire lesion, tissues that are calcified and therefore difficult to adequately section without further processing, and artifacts resulting from the surgical manipulation of the tissue or from poor freezing technique. (These artifacts tend to be particularly problematic in differentiating round cell tumors from infection or spindle cell tumors from exuberant granulation tissue.)
Chapter 3

Imaging Techniques, Interpretation, and Strategies

Sarah J. Jackson
Judith E. Adams

Wilhelm Conrad Röntgen (1845–1923). Röntgen won the first Nobel Prize in Physics in 1901 for his discovery (1895) of electromagnetic radiation in a wavelength range now known as x-rays. Shown next to the portrait of Röntgen is a radiograph of his wife’s hand. When she saw her skeleton, she exclaimed: “I have seen my death!” (From the Wellcome Library, London.)
Imaging plays a very important role in the identification, diagnosis, and management of bone and soft tissue diseases and is essential to good orthopaedic and pathology practice. Radiography is the longest established imaging modality and still remains the cornerstone of musculoskeletal imaging. Definitive diagnoses of many bone and joint disorders, such as fractures, arthritis, and some metabolic disease, can be made from radiographs alone without recourse to more sophisticated techniques.

The range of imaging techniques has expanded over the past 30 to 40 years to include radionuclide (RN) scanning, computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI). CT, MRI, and US have greatly improved the identification and characterization of some entities, especially soft tissue lesions, often not readily visualized on radiographs. These techniques require skill and experience in their execution and interpretation.

For resources and imaging techniques to be used appropriately and effectively, there must be close collaboration between clinician, pathologist, and radiologist, particularly when dealing with potentially malignant bone and soft tissue tumors.

The role of musculoskeletal imaging includes:
- Confirmation of the presence of a skeletal lesion
- Definition of the morphologic characteristics of the lesion
- Performance of sequential investigation in a proper order, to refine the differential diagnosis of individual lesions
- To characterize the features, location, and distribution of skeletal disorders
- Identification of "don’t touch" lesions, including lesions necessitating no further active investigation or treatment
- Recognition of the limits of imaging
- Staging of malignant tumors, and identification of tumor recurrence
- Guidance for invasive procedures, such as targeted biopsy
- Monitoring progress of lesions

Despite sophisticated developments in imaging, there continue to be limitations in tissue-specific diagnoses, particularly regarding tumor types and grades. Therefore, correlation of a patient’s radiologic findings with the histopathologic and clinical assessment remains of paramount importance. Errors are less likely to be made if such teamwork, which relies on effective communication, is practiced.

The biopsy of suspicious lesions should be performed after imaging, because the presence of a cortical defect or hematoma following bone biopsy may erroneously raise the suspicion of malignancy on subsequent imaging. Biopsy of soft tissue lesions should be performed only in consultation with surgeons experienced in the management of soft tissue sarcomas, because an inappropriate approach may adversely affect the subsequent resectability.

**Imaging Methods**

**TECHNIQUES THAT USE IONIZING RADIATION (X-RAYS)**

Radiography

When radiography is undertaken, some x-rays are absorbed, depending on the thickness and the atomic number of the tissues through which they pass; the remainder then exit the body, giving a differential pattern of x-rays, which falls onto the fluorescent screens of the radiographic cassette.

The use of fluorescent screens was an important development; in the past, the formation of a radiographic image relied on the direct interaction between the x-rays and the radiographic film, without the use of screens. Therefore, a much higher dose of radiation was needed to form an image, with greater risk to the patient.

Bone and calcium, give a white, ‘radiodense’ appearance on the radiograph; air and fat, a black, ‘radiolucent,’ appearance; soft tissues such as muscle, show intermediate x-ray transmission and appear gray on the processed film (Fig. 3-1). (CT, US, and MRI may be needed to assess the soft tissue components of lesions.)

Radiographs are two-dimensional (2D) images of three-dimensional (3D) anatomy, with superimposition of overlying structures in the path of the x-ray beam. In order to define clearly the anatomic site and extent of a bone lesion, at least two views (for example anteroposterior and lateral) are needed. Destruction of cortical bone is best seen where the x-ray beam is tangential, rather than perpendicular, to an area of cortical destruction (Fig. 3-2).

Loss of trabecular bone is often more difficult to define. Up to 40% of the trabecular bone may be destroyed before its loss is evident on a radiograph. Therefore, radiography can be insensitive to subtle bone destruction or abnormality (Fig. 3-3). A normal radiograph does not reliably exclude the presence of a bone lesion. Detection of a lesion on radiographs may be particularly difficult in areas of complex anatomy, such as the wrist or foot, or where bone is obscured by overlying structures, such as the sacrum on an anteroposterior view of the pelvis. In these cases, RN bone scanning can be sensitive in identifying that a lesion is present, but may be limited in its specificity for defining the pathologic etiology. Targeted cross-sectional imaging, using CT or MRI, is then useful to subsequently define the pathology, the exact anatomic location, and the extent of the lesion (Fig. 3-4).

When radiographic images are being examined, it is essential to optimize viewing conditions. Radiographs should be viewed on dedicated viewing boxes, with subdued background lighting. A bright light should be available to examine dark areas of the image, and a magnifying glass may be useful, for example in the identification of early bone erosions.

Technologic developments have led to the introduction of digital imaging, in which the image data are processed electronically. Although digital images do not have the high spatial resolution of radiographic film-screen combinations, they have the advantages...
of greater exposure latitude, image enhancement, manipulation, and storage. Digital images can be stored and transmitted electronically, providing the basis of filmless picture archiving and communication systems, or can be printed on film if required.

Techniques that use ionizing radiation must be performed only when there is clinical justification. Dose minimization techniques should be used with gonadal shielding when possible, particularly in children and young adults. Examinations should be tailored to the clinical indication, and unnecessary repetition should be avoided, because all ionizing radiation examinations carry an element of risk.

**Computed Tomography**

CT of the head transformed the practice of neuroradiology following its introduction in 1972 for brain imaging, and the potential for imaging other parts of the body was soon realized. Body CT
Scanners were introduced in 1975, with one of their important clinical applications being in musculoskeletal disorders.

In CT, the x-ray beam is finely collimated, giving a fan-shaped beam with typical slice widths of 1 to 10 mm. The x-ray tube rotates around the patient, and sensitive detectors record the x-rays that pass through the body. Powerful computers use the pattern of exiting x-rays to construct an image. This is viewed as a gray scale image, with the varying shades from black to white representing the range of x-ray attenuations of the tissues.

Tissues with high atomic number and x-ray attenuation values, such as bone, appear white; low attenuation areas, such as air and fat, appear dark; and other soft tissues, such as muscle, are depicted as shades of gray. The attenuation value of each picture and volume element (pixel and voxel respectively) of the image can be described using Hounsfield units (HU). These form a numeric scale that uses the attenuation of x-rays by water as a reference point (0 HU), and that has both positive (e.g., bone: 250 to 1000 HU) and negative (e.g., fat: –100 HU; air: –600 HU) values. A wide range of attenuation values can be measured on CT, whereas the human eye can appreciate only limited shades of gray. The attenuation level (window level—mid range of attenuations being viewed) and range (the window width is the range of attenuations being viewed) must therefore be altered to optimize viewing of different tissue types within the constraints of a visual image. The use of appropriate window settings and interrogation of the CT images on a workstation, rather than relying on hard copy images (those recorded on film) for reporting, is essential to avoid missing lesions. To visualize soft tissues, the window level would be set at 50 HU and the window width would be 500 HU; to visualize bone the window level might be set at 250 HU with a wide window width of 1000 HU, and when viewing the air-filled lungs, the window level would be in the region of –600 HU with a window width of 1000 HU (Fig. 3-5).

The use of contrast agents can aid diagnosis in CT. Contrast media can be administered, for example, intrathecally to give a CT myelogram, or into joints to give CT arthrography.

The advantages of CT include the following:

- The ability to display cross-sectional anatomic data on CT transverse sections, which overcomes the problem of overlapping structures on 2D radiography
- CT is better than radiography for soft tissue imaging (but not as good as MRI), because it has higher soft tissue contrast sensitivity
- CT imaging protocols can be optimized for specific clinical scenarios
- Quantitative data on composition (e.g., bone densitometry), dimensions, or contrast enhancement can be provided
- Data can be manipulated to give multiplanar reconstructions (coronal, sagittal) or 3D images
- CT is good for assessing cortical bone

The disadvantages of CT include

- The use of significant doses of ionizing radiation; CT currently contributes a major proportion of medical radiation exposure
- Inferior soft tissue contrast resolution compared with that of MRI.

Technologic advancements of continuous spiral and multi-slice imaging have led to reduced examination times and have also provided improved longitudinal spatial resolution, dynamic contrast enhanced scanning, and 3D volume acquisition (Fig. 3-6).
Radionuclide Scanning

RN bone scanning was introduced in the early 1960s. Since that time, developments in radiopharmaceutical agents and scanning techniques have led to significant improvements in the spatial resolution of RN scan images.

In RN bone scanning, technetium-99m is used to label phosphate compounds, such as methylene diphosphonate ($^{99m}$Tc-MDP), which is then administered intravenously. $^{99m}$Tc-MDP is chemically absorbed onto hydroxyapatite crystals in bone. Its uptake is a reflection primarily of osteoblastic activity, but is also dependent on vascularity. Approximately 70% of the administered dose of RN is excreted through the kidneys within 24 hours. Radiation exposure to the bladder can be minimized by good hydration of the patient and frequent micturition.

Photon emission from the whole skeleton or localized sites can be recorded using a scintillation camera. Initially, the radiopharmaceutical can be detected intravascularly, before pooling in soft tissues and then being taken up in bone, over approximately 2 hours, where 50% of injected $^{99m}$Tc-MDP localizes. This can be imaged as a ‘triple phase’ examination, with images obtained immediately (the flow images), after a few minutes (the blood pool images), and after approximately 4 hours (the static images) (Fig. 3-7). Depending on the indication for the scan, only the static images may be necessary.

RN scanning is very sensitive to abnormalities in the skeleton. Any process that alters the balance between bone resorption and bone formation can cause abnormalities on the bone scan, with regions of increased osteoblastic activity (‘hot spots’) or decreased activity (‘cold spots’). RN scanning is very useful in the detection of pathologic changes at a symptomatic site, when radiography has shown no abnormality, because even small areas of increased activity are easy to detect.

Because a wide variety of conditions, both normal (epiphyses and metaphyses of the growth plate in children) and pathologic (primary and secondary bone tumors, osteomyelitis, fractures, metabolic bone disease and arthropathy), may show increased activity, RN scanning is nonspecific. The distribution of abnormality may suggest particular processes: for example, multiple ‘hot spots’ throughout the skeleton in the presence of normal radiography suggest metastases (Fig. 3-8A), diffuse enlargement and increased activity of a single bone occurs in Paget’s disease, and focal abnormalities adjacent to joints may represent degenerative arthritis with hyperostosis (Fig. 3-9).

Single photon emission computed tomography applies tomographic technology to RN scanning, enabling a cross-sectional image to be obtained. This enhances the conspicuity of lesions and is useful in their localization.

Positron-emission tomography (PET) uses positron emitting radioisotopes. The RN most frequently used is F-18 deoxyglucose (FDG), which is taken up in cells proportionally to the rate of glycolysis in the cell. Malignant tumors, inflammation, and other conditions of high metabolic turnover therefore have increased uptake of FDG. In addition, because malignant tumors have a decreased ability to break down the byproduct of FDG, it is trapped in the cells and can be seen on a scintigram as an area of increased uptake. The scintigram is often combined with simultaneous CT (PET CT) for exact localization of the sites of increased uptake (see Fig. 3-8B). PET-FDG scanning is used mainly in detecting soft tissue and skeletal metastases. PET may be useful in differentiating benign from malignant lesions. In some cases, however, some benign conditions with high metabolic activity, such as osteomyelitis and Paget’s disease, may have high uptake, whereas some malignant lesions may have lower metabolic turnover, such as some osteoblastic metastases, and may not show high uptake.

![Figure 3-7](image)

**Figure 3-7** Three-phase radionuclide scan in a patient who has Charcot changes in the midfoot portion of both feet and osteomyelitis involving the first metatarsophalangeal joint of the right foot. Images have been obtained immediately (the flow images) (A); after a few minutes (the blood pool images) (B), and after approximately 4 hours (the static images) (plantar view) (C). There is increased blood flow and increased uptake of radionuclide in the bones of the mid-part of each foot (due to Charcot changes) and in the area of infection in the right foot. (Courtesy of Dr. Mary Prescott, Consultant Nuclear Medicine Physician, Manchester Royal Infirmary, UK.)
The advantages of RN scanning include

- High sensitivity to increases in bone turnover
- A good survey technique for abnormality anywhere in the skeleton
- A role in the initial localization of bone lesions, enabling further imaging by other modalities to be targeted to the relevant anatomic site

The disadvantages of RN scanning include

- Poor spatial resolution
- Nonspecific appearances for areas of increased activity
- False-negative scans in myeloma and osteoclastic metastases
- Relatively high radiation dose, particularly to bone marrow, and in children.

TECHNIQUES THAT DO NOT USE IONIZING RADIATION

Ultrasonography

This technique has been in use since the late 1960s, initially in obstetric and antenatal practice. Its use has now disseminated to almost all radiologic fields, with increasing musculoskeletal applications. US equipment has the advantages of being relatively inexpensive, small, and mobile when compared with other imaging hardware but is highly dependent for acquisition and interpretation of the US images on the expertise of the operator.

During an US scan, sound waves are emitted from a transducer held against the skin surface. The use of lubricating gel couples the transducer to the patient, allowing the transmission of the sound waves into the body. The US waves are reflected at tissue interfaces within the patient and are detected back at the transducer. By timing the period elapsed from emission of the sound waves to the detection by the transducer, the depth to the echo-producing structure can be calculated. This information is displayed on a screen and can be recorded digitally or by using film, video, or thermal paper images. The use of the Doppler principle enables qualitative and quantitative observation of vascularity and blood flow.
Not all of the sound waves are detected back at the transducer; some are lost due to scatter, absorption, and reflection within the tissues. This attenuation depends partly on the frequency of the waves: high-frequency waves show greater absorption than low-frequency waves. High-frequency US has the advantage of good spatial resolution, but because of high attenuation, can be used only to visualize superficial structures. If deeper structures are to be visualized, lower frequency US has to be used, at the cost of poorer spatial resolution. Frequencies most commonly used for routine ultrasonography range between 3 and 14 MHz.

The examination of tendons is one of the commonest indications for musculoskeletal sonography, particularly around the shoulder, ankle, and wrist. Normal tendons have an echogenic, fibrillar structure in the longitudinal plane and are ovoid in cross-section (Fig. 3-10). US has the considerable advantage over MRI tendon scanning of allowing dynamic examination of these structures, with easy comparison with the contralateral limb.

US is also useful to confirm or refute the presence of a mass, whether perceived or occult. Cystic lesions are clearly distinguishable from solid lesions by their hypo/anechoic appearances, their compressibility, and the presence of posterior acoustic enhancement. Their location and relationships may suggest specific diagnoses, such as parameniscal cysts. Many masses have nonspecific US appearances, whereas a few have more characteristic appearances. Neuromata, for example, are typically hypoechoic with a fusiform shape and a neural ‘tail’ leading to and from the lesion. The presence of sinister clinical features, such as rapid growth or onset of pain, may necessitate examination with another modality, such as MRI, to examine for evidence of malignant pathology.

The sensitivity of US to the detection of fluid makes it particularly useful in the confirmation of joint effusions, particularly in deep joints such as the hip and the shoulder. US provides a useful technique for guided aspiration of effusions, and can also be used for real-time guidance of other procedures, such as therapeutic injections and soft tissue biopsies.

The advantages of US include
- Relatively low cost, compared with MRI and CT
- Multiplanar imaging
- The ability to perform dynamic scanning on active and passive movements (tendons, muscles, joints)
- Relatively portable and easily transportable equipment

- A high level of patient acceptability
- No use of ionizing radiation
- Harmless at the intensities used in clinical practice.

The disadvantages of US include
- Reliance on the skill and expertise of the operator in acquisition and interpretation of the images
- A long learning curve for developing skill in performing musculoskeletal US imaging and a relative lack of training opportunities in performing such scanning
- Relatively limited information gleaned of the pathologic composition of solid tumors
- The images being of limited value for objective interpretation by those who have not themselves performed the scans. This limits clinical acceptance of the technique and so slows changes in practice by referring clinicians who may not be familiar with US.

**Magnetic Resonance Imaging**

MRI employs magnetic fields and radiowaves rather than ionizing radiation. Materials placed in a magnetic field can absorb and re-emit radiowaves of a specific frequency. The application of magnetic fields and excitation radiofrequency pulses to a patient, with detection of the signal emitted from the tissues of interest, can be used to build up an image.

Most MRI sequences are tuned to detect hydrogen nuclei in water (protons). Therefore, images reflect the relative concentrations of protons in tissues by measuring the signals from individual volumes of tissue (voxels) in the patient and displaying these as a gray-scale image.

Each proton spins, like a top, around an axis. In the absence of a magnetic field, these axes are randomly orientated and produce no net magnetic effect. Inside the MRI scanner, the static magnetic field causes the axes of rotation of the protons to align with the long axis of the magnet, with a slight excess orientated parallel to the field. As well as spinning, the protons also ‘wobble’, or precess, around their long axes with a fixed frequency. The tilt in the spin axis of a proton splits its magnetization vector into both longitudinal and transverse components.

During MRI, radiofrequency pulses and magnetic field gradients are used to re-align the axes of rotation of the spinning protons.

---

**FIGURE 3-10** Ultrasound of tendons. A, Longitudinal scan of Achilles’ tendon in a patient with rheumatoid arthritis showing the fibrillar, echogenic structure of the tendon (arrows), above which is a less echogenic oval structure, which is a rheumatoid nodule. B, Transverse scans of the wrist showing the flexor tendon (FT) and the median nerve (MN); note that the tendon is more echogenic than the nerve.
and to pull their precession into step, or phase, with each other. When the excitation pulse is over, the protons spinning at an angle to the longitudinal axis of the scanner act like rotating magnets in a dynamo, inducing a tiny current in the surrounding coil, which can be detected and amplified to give a signal, and hence an image. The spinning protons then return to their original orientation.

Longitudinal relaxation occurs as their spin axes realign to the long axis of the magnet. $T_1$ is defined as the time taken for the longitudinal magnetization vector to recover to 63% of its maximal value. This value varies, depending on how quickly protons give up energy to their surroundings. The greater the proportion of free water in a tissue, the longer the $T_1$ value for that tissue. As the precessing protons dephase, the transverse component of the magnetization vector decreases exponentially, with decrease in signal. $T_2$ is defined as the time taken for the MRI signal to fall to 37% of its maximal value. The $T_2$ value is always shorter than the $T_1$ value of a tissue, and it is also longest in tissues with a high proportion of free water, where there is less 'spin-spin' interaction.

The $T_1$ and $T_2$ values vary for different tissues and therefore are used for forming the image. The timing of excitation pulses and the collection of signal enable different sequence weighting. $T_1$-weighted images give maximum contrast between tissues dependent on proton density and $T_1$ values, with fat being of high signal (bright, white signal) and fluid being low in signal (dark, black signal). $T_2$-weighted images use longer times to detection of signal and reflect $T_2$ contrast differences between tissues, with fluid being brighter than fat. The relative signals of some different tissues on $T_1$- and $T_2$-weighted images are shown in Table 3-1, and those of hemorrhage are given in Table 3-2. The signal characteristics of hemorrhage depend on the presence of different blood products according to the age of the bleed.

Intravenous MR contrast media containing chelated gadolinium (Gd DTPA) cause increased signal on $T_1$-weighted images due to a paramagnetic effect. They are water-soluble and are used to produce increased ('positive') contrast between areas of high uptake and the surrounding tissues (Fig. 3-11). ‘Negative’ contrast media, such as iron oxide particles, are also used. These rely on ferromagnetic effects and give reduced signal in areas of uptake.

A great number of MRI sequences have been developed to potentiate tissue contrast, and enhance the conspicuity of pathologic lesions. Short tau inversion recovery sequences, for example, have a pulse designed to suppress the high signal from fat, making high signal fluid and edema more conspicuous, and pathologic lesions more obvious (Fig. 3-12).

The high contrast sensitivity of MRI makes it the modality of choice for defining the soft tissue margins of tumors and marrow changes within bones. Therefore, it is an important method of imaging the extent of tumors. MRI scans do give some indication of the pathologic nature of lesions, but they may be nonspecific; edema, for example, is high signal, whatever the cause.

The advantages of MRI include

- The capacity to image in any anatomic plane (multiplanar imaging)
- High soft tissue contrast, with some indication of tissue composition
- No use of ionizing radiation
- Acquisition of 3D volume data using gradient echo sequences, with potential for multiplanar display
- Noninvasive imaging of blood vessels and other structures (e.g., bile and pancreatic ducts in MR cholangiopancreatography), without the use of contrast media or interventional methods.

The disadvantages of MRI include

- The high cost of equipment
- Problems with image artifact from motion (e.g., of bowel, heart, and respiration) and ferromagnetic objects
- Not as good as CT for imaging cortical bone
- Contraindications to use (cardiac pacemakers, some cerebral aneurysm clips, claustrophobia, first trimester of pregnancy, metallic foreign body in eye)

### Morphologic Abnormalities of Bone

The recognition of abnormal bone appearances is foremost in skeletal radiology, and requires familiarity and experience to enable distinction between a pathologic lesion and the wide range of radiographic normality. Patient demographics, and clinical and laboratory data are important in placing the imaging features into context.

### TABLE 3-1 Signal Intensities of Tissues of the Musculoskeletal System on $T_1$- and $T_2$-Weighted Magnetic Resonance Images (MRI)*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Signal—$T_1$-Weighted Image</th>
<th>Signal—$T_2$-Weighted Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Fat</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Muscle</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Bone cortex</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Structures of low signal intensity appear black in the image, those of high signal intensity appear white, and those of intermediate signal intensity appear in ranges of gray between these two extremes.

### TABLE 3-2 The Signal Intensities of Hemorrhage on Magnetic Resonance Images (MRIs), on $T_1$-Weighted ($T_1$-W) or $T_2$-Weighted ($T_2$-W) Sequences*

<table>
<thead>
<tr>
<th>Age of Hemorrhage</th>
<th>Approximate Time</th>
<th>Blood Product</th>
<th>$T_1$-W Signal</th>
<th>$T_2$-W Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>&lt; 24 hours</td>
<td>Oxymyoglobin</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Acute</td>
<td>1–3 days</td>
<td>Deoxymyoglobin</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Subacute – early</td>
<td>&gt; 3 days</td>
<td>Intracellular methemoglobin</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Subacute – late</td>
<td>&gt; 7 days</td>
<td>Extracellular methemoglobin</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Chronic</td>
<td>&gt; 14 days</td>
<td>Hemosiderin/ferritin</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Areas that give a high signal appear white, those that give a low signal appear black, and those that give an intermediate signal are seen as shades of gray.
The following section aims to illustrate an approach to morphologic abnormalities of bone. Examples of characteristic distinguishing features are provided, rather than an exhaustive list of multiple conditions, which are covered elsewhere in this book.

**SCLEROSIS**

Sclerosis is seen on radiographs as an increase in bony density (white). Increased density may be generalized, regional, or focal.

**Generalized Sclerosis**

Generalized osteosclerosis results from a range of conditions, but the identification of specific features helps to refute or confirm particular diagnoses. Osteopetrosis is a dysplastic condition associated with abnormal bone modeling and generalized increase in bone density (Fig. 3-13). A 'bone within a bone' appearance is characteristic of this condition. Myelofibrosis, in which progressive fibrosis of the bone marrow in middle-aged patients causes generalized bony sclerosis, is associated with splenomegaly and extramedullary hematopoiesis. Patients with fluorosis often have, in addition to sclerosis, ossification of ligaments (enthesopathy).

**Regional Sclerosis**

Paget’s disease is a classic cause of regional osteosclerosis. The disease can affect any bone, single or multiple, but occurs most often in the skull, axial skeleton, extremities, and pelvis, with characteristic
thickening of the ilio-pectineal line; bone expansion and a disordered trabecular pattern are typical findings (Fig. 3-14). (In the early phase of the disease, there can be a lytic, or mixed lytic and sclerotic, appearance.) Characteristically, Paget’s disease extends from the end of a long bone, often with a ‘flame-shaped’ leading edge (cortical splitting). Bone fragility results in bowing of weight-bearing bones, with incremental fractures on the outer, convex margin.

**Patchy/Focal Sclerosis**

The multiplicity and distribution of focal sclerotic lesions are useful in diagnosis. Osteoblastic metastases, most commonly from bronchial, prostatic, and breast primary cancers, are usually multiple. In osteopoikilosis, the distribution of uniformly well-defined, small lesions in the ends of long bones is characteristic. Melorheostosis is a rare osteosclerotic dysplasia in which there are irregular masses of sclerotic bone that ‘flow’ like ‘dripping candle wax’ from the bones of the limbs (Fig. 3-15).

**OSTEOPENIA**

**Generalized Osteopenia**

A decrease in radiographic bone density reflects either decreased quantity of bone (osteoporosis) or defective mineralization (reduced calcium per unit volume) of bone (osteomalacia).
Osteoporosis, seen most often in post-menopausal women, is a deficiency in the quantity of bone, resulting either from defective bone formation or an imbalance between bone accretion and resorption.

Radiographically, there is thinning of the bony cortices and resorption of secondary trabeculae, with prominence of remaining trabeculae giving vertical striations, particularly in the vertebral bodies. As a consequence, fractures occur with little or no trauma (insufficiency fractures), particularly in the spine, proximal femur, and distal radius. In the spine, fractures result in wedge, end-plate, or crush deformity of the vertebrae causing thoracic kyphosis and loss of height (Fig. 3-16). The diagnosis of osteoporosis from radiographs is unreliable in the absence of fractures, and therefore, quantitative measurements of bone density have been developed such as dual energy x-ray absorptiometry and quantitative computed tomography. These methods can be applied to measure bone mineral density in axial and peripheral skeletal sites.

Osteomalacia, or defective bone mineralization, is another cause of generalized osteopenia in both adults and children. In childhood, the pathognomonic features of rickets relate to defective enchondral ossification and are evident at the metaphyses (Fig. 3-17). In adults, osteomalacia causes the diagnostic Looser’s zone (Fig. 3-18). This linear lucent lesion is most often seen in the medial border of the femoral neck but may also be seen in the pubic rami, lateral border of the scapulae, and ribs. Looser’s zones occur perpendicular to the cortex, often have a sclerotic margin, and can extend right across the affected bone, but heal with appropriate treatment.

**Regional Osteopenia**

Regional osteopenia often results from immobilization or disuse, such as after a fracture or immobilization, or both. This disuse osteoporosis occurs more rapidly than senile osteoporosis. The bone has a patchy, almost permeative, appearance, caused by osteoclastic bone resorption in the cortex and hyperemia. In reflex sympathetic dystrophy (Sudeck’s atrophy), a similar appearance can follow even relatively minor local or regional trauma and is accompanied by pain and soft tissue swelling. There is increased uptake of RN on bone scan (Fig. 3-19).
Transient osteoporosis of the hip is a rare disorder first described in women during the last trimester of pregnancy but actually seen most often in middle-aged men. The disease is characterized clinically by pain in the affected hip. Radiographically, there is osteopenia with no joint space narrowing, in the absence of other causes of synovitis or osteoporosis. Within a few months, the pain and the radiologic abnormalities may resolve spontaneously. MRI and RN bone scans are sensitive imaging techniques to identify this entity at an early stage.

ABNORMAL TRABECULAR PATTERN
An abnormal trabecular pattern is rarely seen in isolation; it usually occurs with abnormal bone density or shape (Fig. 3-20).

Generalized Abnormal Trabecular Pattern
Conditions that result in marrow expansion, such as lipid storage disorders and hemoglobinopathies, cause abnormal trabecular appearances. Identification of the typical radiographic and demographic features assist in defining the specific diagnosis. In Gaucher’s disease, most prevalent in Ashkenazi Jews, abnormal accumulation of lipid occurs in the reticuloendothelial cells. In the bones, this results in endosteal cortical scalloping, resorption of spongy trabeculae and osteopenia. Erlenmeyer flask deformities of the distal femora are characteristic, and fractures, osteonecrosis, and infection may occur.

Patients with hemoglobinopathies share some features of Gaucher’s disease. The bones may lose their normal tubulation

![Figure 3-18 Osteomalacia](image)

Looser’s zones seen here in the forearm are horizontal translucent zones with sclerotic margins. Usual sites include the femoral necks, pubic rami, lateral borders of the scapulae, and ribs. Complete fractures can extend through Looser’s zones, and these heal with appropriate treatment.

![Figure 3-19 Sudeck’s reflex sympathetic dystrophy in the right foot](image)

A, Radiograph of the feet show that the bones of the right foot are reduced in density when compared to the left foot. Three-phase radionuclide scans: immediate—blood flow (B) and blood pool phases (C), respectively, show increased uptake in the right foot due to hyperemia and increased bone turnover.
Chapter 3
Imaging Techniques, Interpretation, and Strategies

(narrow shafts with wider ends) and show a net-like trabecular pattern caused by expansion of the marrow cavity (Fig. 3-21). In the skull, marrow expansion causes thickening of the vault, with a ‘hair on end appearance’. Bone infarcts occur in sickle cell diseases and these can result in shortened and distorted bones if they involve the growth plate of the immature skeleton (Fig. 3-22).

Focal Abnormal Trabecular Pattern

Focal bone lesions can also be associated with trabecular abnormality. Hemangiomata, for example, show a striated pattern on radiography, especially when involving the vertebral body. These lesions show a spotty appearance on transaxial CT, caused by sectioning across the thickened, vertical trabeculae, and have characteristic fat signal on MRI (Fig. 3-23).

In the context of trauma, a focal abnormality of the trabecular pattern may be the only radiographic sign of fracture. This is particularly true in children, whose bones are relatively elastic and can fracture with plastic deformation of the bone without a visible cortical break. In adults, a band of relative sclerosis in a bone may reflect an impacted fracture, often less easily recognized than the more familiar lucent fracture line. Some fractures may be subtle and not identified on radiographs; in such cases, MRI, or alternatively RN scanning, are more sensitive techniques for confirming the presence of fracture, particularly in sites such as the femoral neck and scaphoid.

Bone Tumors and Tumor-Like Bone Lesions

Patients with bone tumors can present to clinicians of various disciplines, most frequently to orthopaedic and emergency departments. Timely interpretation of radiologic examinations by appropriately trained personnel is important. Systematic review of the images is required to define the nature and extent of lesions and determine whether additional imaging is indicated.

Some bone tumors may be discovered incidentally when a radiograph is performed for another purpose. Alternatively, both benign and malignant lesions may present with acute pain or a pathologic fracture. Certain tumors (e.g., osteoid osteoma) present with chronic pain, whereas aggressive malignant lesions often present as an enlarging mass. In the context of localized symptoms and signs, radiographs are performed of the relevant anatomic site.
The following features are of particular note in the differentiation of bone tumors:

- Patient age
- Anatomic site
- Margins of the lesion
- Cortical bone appearances
- Periosteal reaction
- Presence of a soft tissue mass
- Presence of tumor matrix calcification or ossification
- Whether the lesion is single, or multiple
- Family history and predisposing conditions.

**PATIENT AGE**

Primary bone tumors occur within characteristic age distributions (Table 3-3). For example, benign chondrogenic, osteogenic, and fibrogenic tumors occur in the bones of children and young adults.
Certain malignant tumors, such as osteosarcoma and Ewing’s sarcoma, characteristically occur in the first 30 years of life. Other lesions, such as chondrosarcoma and myeloma, are much more common later in life.

### SITE OF SKELETAL INVOLVEMENT

Bone tumors occur frequently in characteristic anatomic sites. For example, 50% of benign chondromas involve the small bones of the hands and feet (Fig. 3-24); giant cell tumor and primary osteosarcomas commonly occur around the knee; chordomas occur exclusively in relation to the midline axial skeleton.

The position of the lesion in bone can also suggest the nature of its pathology: giant cell tumors are typically juxta-articular and eccentric; chondroblastomas arise in epiphyses (Fig. 3-25); chondromyxoid fibromas are typically located in the metaphyses of long bones. Osteosarcomas may arise either centrally or on the surface of the bone. Cartilage-capped exostoses tend to occur at the ends of long bones, because they are related to abnormalities of enchondral ossification and are directed away from the adjacent growing end of the bone.

### MARGINS OF LESION

A narrow zone of transition between an area of bone destruction and normal bone, and a thin sclerotic or corticated rim are suggestive of a benign etiology, such as an enchondroma or nonossifying fibroma (Fig. 3-26). The more aggressive or malignant a bone lesion, the wider and less distinct will be the transition zone between destruction and normal bone (Fig. 3-27). Bone destruction may have a permeative or ‘moth-eaten’ pattern of destruction that is also indicative of an aggressive lesion (Fig. 3-28).

Some locally aggressive lesions, such as giant cell tumors and aneurysmal bone cysts, may have marginal features intermediate between these two extremes (Fig. 3-29).

---

**TABLE 3-3** Bone and Soft Tissue Tumors Showing Characteristic Peaks in Incidence at Different Ages

<table>
<thead>
<tr>
<th>Decade of Life</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
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<tbody>
<tr>
<td>Simple bone cyst</td>
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<tr>
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<tr>
<td>Nonossifying fibroma</td>
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<td>Fibrosarcoma and malignant fibrous histiocytoma</td>
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CORTICAL BONE APPEARANCES

Benign lesions may cause some endosteal erosion of the bone cortex but generally cause little expansion. If bone expansion does occur in benign lesions, a thin shell of cortex is usually retained. Disruption of the cortical rim can occur in benign lesions if a pathologic fracture has occurred, which may make differentiation between a benign or malignant pathology more difficult.

Aggressive and malignant lesions erode and destroy the bone cortex. When this occurs, often there is an associated periosteal reaction and a soft tissue mass is present.
A periosteal reaction in benign tumors is unusual, unless a pathologic fracture has occurred.

An aggressive, rapidly growing tumor arising within a bone extends into adjacent structures as a soft tissue mass over a short period. The use of imaging is important to define this extension. Such local staging is necessary to determine whether resection and limb salvage are feasible. MRI is the modality of choice for such local staging (Fig. 3-31).

**TUMOR MATRIX CALCIFICATION AND OSSIFICATION**

In benign bony lesions (osteoma, osteochondroma), matrix mineralization is ordered, forming trabeculae that can be traced from the tumor, through its margin, into the surrounding bone from which it arises (Fig. 3-32). The matrix of malignant osteosarcoma may also mineralize, but this occurs in a more haphazard fashion, forming clumps or ‘sunray’ spicules of calcification (see Fig. 3-30B).

Cartilaginous tumors are generally radiolucent on radiographs but can form well-defined conglomerate clumps of matrix calcification, seen as broken rings or snowflake shapes, often located centrally in the tumor (Fig. 3-33). Fibrous tumors generally do not contain calcification that is visible on radiographs. In fibrous dysplasia the bone lesions may have a hazy, ‘ground-glass,’ appearance because they contain an abundance of small osseous trabeculae intermingled with fibrous tissue. These lesions can expand bone and cause sclerosis (Fig. 3-34).

**FAMILY HISTORY AND PRE-EXISTING CONDITIONS**

In the small number of patients with multiple exostoses (diaphyseal aclasia), there is a strong family tendency and a higher incidence of chondrosarcoma (up to 27%) (Fig. 3-35).

Specific clinical features may be associated with certain skeletal abnormalities. For example, in McCune-Albright’s syndrome, polyostotic fibrous dysplasia is associated with precocious puberty and skin pigmentation.
Imaging Strategies in Bone Lesions, with Particular Emphasis on Bone Tumors

CLINICAL PRESENTATION

Asymptomatic Presentation

Bone lesions are commonly identified as an incidental finding on a radiograph performed for other clinical reasons, such as trauma. From the radiographic appearances, it may occasionally be possible to make a diagnosis. If appearances are indeterminate, comparison with any previous imaging may enable assessment of any interval change. A lesion showing no change over a period of years is likely to be benign, requiring no further action. It is important that normal variants, such as accessory ossification centers or asymmetric closure of synchondroses, are not misdiagnosed as significant bone pathologies (Fig. 3-36).

If the radiographic appearances of the lesion remain indeterminate, or if sinister pathology is suspected, further action is essential. A detailed clinical history and thorough physical examination of the patient should be made before embarking on further imaging, because these may reveal symptoms or signs relevant to the diagnosis: for example, a history of cancer or a palpable primary tumor suggests that a bone lesion is likely to be a metastasis.

In the absence of relevant history or abnormal physical signs, further imaging will be needed to determine the nature of the lesion. This may include MRI (or CT) to define additional features, helping to differentiate between benign and malignant pathologies. Alternatively, an RN scan may be appropriate to assess whether the lesion is single or multiple. The need for additional imaging, and its appropriate sequence is best determined by discussion between the clinician and the radiologist.

Ideally, the pathologist should also be involved: biopsy may be needed to make a definitive histologic diagnosis, and familiarity with the history and radiographic findings is helpful in pathologic diagnosis. A strong case has been made for regular multidisciplinary meetings between clinicians, radiologists, and pathologists to enhance the cooperative diagnosis and management of patients with bone tumors, and to extend the education and experience of those involved in their care. It is regrettable that this does not always happen.

Presentation with Acute Pain

Acute pain is most likely to be caused by a fracture, which may be pathologic and occur through an existing bone lesion (see Fig. 3-28). The symptomatic site should be radiographed with at least two views at right angles, and with supplementary specialized projections as needed to make a diagnosis.
appropriate. The radiographic appearances may be diagnostic of a benign lesion, (e.g., simple bone cyst or enchondroma).

If the fracture has occurred through an aggressive lesion, further imaging may be relevant and biopsy is likely to be required, particularly if the lesion is solitary. The presence of a fracture may confuse both the imaging and histopathologic interpretation. The pathologist should always be informed of the presence of a fracture through a bone lesion and the site from which the biopsy was taken.

**Presentation with Chronic Pain**

Radiography of the symptomatic site forms the baseline imaging investigation. In the context of genuine symptoms and abnormal physical signs, such as tenderness or swelling, without demonstrable radiographic abnormality, further imaging is appropriate.

In this situation, RN scans have been used as a screening method to identify any area of increased bone activity. If an RN scan is normal, a significant bone lesion is highly unlikely and the patient may be reassured.

CT is particularly useful in showing fine bone detail. For this reason, CT is superior to MRI in the diagnosis of osteoid osteoma (Fig. 3-37). Neither radiographs nor RN scanning permit accurate localization of the nidus of an osteoid osteoma in the context of extensive reactive sclerosis. In the absence of radiographic abnormality, RN scanning or MRI can be used to define the site and size of bone abnormality. Thin section CT is then used to provide precise detail of the nidus and can now be used to direct percutaneous radio ablation as an alternative to open surgery.
If the radiograph shows the characteristic features of a benign bone lesion, appropriate treatment can be planned. Cross-sectional imaging (using CT or MRI) may provide additional valuable information to the surgeon. This information might include the exact site and extent of the lesion in three dimensions and the relationships of the lesion to adjacent articular surfaces and other anatomic structures, such as neurovascular bundles, all of which will influence the feasibility, approach, and extent of surgery. Histologic confirmation of the diagnosis may be obtained before or during surgery.

**Suspected Bone Metastases**

If the radiographic features suggest a malignant lesion, a distinction must be made between a primary bone tumor and metastases. RN scanning can confirm the presence of metastases by the presence of multiple ‘hot spots’ in a characteristic distribution throughout the skeleton, in which case no further imaging is required, particularly if the patient is known to have a primary malignant tumor.

If there is a solitary bone lesion that is suspicious, but not diagnostic, of a metastasis, biopsy is performed for histologic confirmation.
Figure 3-37  A to C, A 17-year-old boy presented with a history of 18-months' pain in his right leg. A, Radiograph showed diffuse sclerosis and periosteal reaction in the medial aspect of the tibial shaft. B, Radionuclide scan shows extensive increased uptake in the proximal tibia. C, Computed tomography (CT) scans (thin sections, 1 to 2 mm) identified the characteristic features of an osteoid osteoma (low-attenuation nidus with central mineralization within the sclerotic bone), and extensive adjacent endosteal and periosteal sclerosis. D and E, An 18-year-old patient presented with backache. Radiographs showed no abnormality. A radionuclide scan (D) shows localized increased uptake in the thoracic spine, and (E) CT confirms the characteristic appearance of an osteoid osteoma in the vertebral lamina on the right.
and to determine subsequent clinical management. Biopsy may be performed using either image guidance, usually with CT (Fig. 3-38) or fluoroscopy, or an open surgical technique.

**PRIMARY MALIGNANT BONE TUMORS**

The principal role of imaging, once features of a primary malignant bone tumor have been confirmed, is in tumor staging, both local and distant. Certain imaging features may suggest the tissue of origin, such as the matrix ossification of osteosarcoma or the ill-defined calcification within a soft tissue mass of chondrosarcoma, but biopsy will be necessary to confirm the histologic diagnosis.

**Initial Staging**

Imaging plays an important role in the initial staging of bone tumors. It is useful in determining the potential resectability of the tumor by defining its extent and showing any involvement of vital anatomic structures (such as neurovascular structures and major organs) that would exclude radical, but potentially curative, surgery.

In order to plan the appropriate surgical excision and endoprosthesis, the surgeon managing such tumors requires accurate information of the intramedullary tumor component, the presence of any satellite lesions, and the extent of soft tissue tumor invasion in relation to the neurovascular structures and surrounding joints. MRI best provides this information. CT may be substituted if MRI is unavailable, but the definition of the tumor or soft tissue interface and marrow involvement demonstrated by CT is inferior to that of MRI.

Malignant bone tumors most commonly metastasize to the lungs. High-quality posteroanterior and lateral projections of the chest must be performed as part of the initial staging procedure. No other thoracic imaging is required if multiple pulmonary metastases are clearly identified on the chest radiograph. However, the chest radiograph is not sensitive to the identification of small lung nodules, particularly those sited in the paravertebral and retrocardiac regions, or in the posterior costophrenic recesses. Therefore, a normal chest radiograph does not exclude the presence of lung metastases. Thoracic CT, the most sensitive method of detecting pulmonary metastases, should be performed if the chest radiograph is normal, or if a single pulmonary nodule of uncertain etiology is present (Fig. 3-39). MRI is not helpful in the identification of pulmonary metastases.

RN scanning is also carried out as part of osteosarcoma staging. Increased activity is present at the site of the primary tumor, with synchronous and metachronous tumors and bone metastases also evident as areas of increased skeletal uptake of RN. Such increased uptake may also be evident in osteogenic metastases in the lymph nodes and lungs.

**Assessment of Treatment Response**

Adjuvant chemotherapy is used in the treatment of some malignant bone tumors, such as osteosarcoma, before surgical resection. Imaging, including MRI of the tumor and radiography or CT of the chest, is performed at initial staging and on completion of the course of chemotherapy. Assessment of the response to treatment is made in terms of reduction in size of the primary lesion and any regression of metastases. A reduction of 50% or more of the primary tumor volume and the development of heavy tumor matrix calcification after chemotherapy generally indicate a more favorable prognosis and may make the tumor easier to resect.

**Follow-Up**

Imaging is used in the surveillance that follows resection. Postoperative imaging is usually deferred for at least 3 months after surgery, because postoperative changes may be misinterpreted as tumor recurrence. Even after this time, it can be difficult to distinguish between tumor recurrence and postoperative changes. The metal endoprostheses that are inserted at limb salvage surgery cause considerable artifact both on MRI and CT, but useful information can nonetheless still be obtained with these imaging methods (Fig. 3-40).

**Image-Guided Biopsy and Therapy**

Most bone neoplasms require biopsy for histologic confirmation of the diagnosis. Biopsy can be performed at surgery (‘open’) or percutaneously (‘closed’), either with image-guidance or without (‘blind’). Imaging can be used to identify the optimum site from which to obtain a tissue sample by avoiding predominantly necrotic or cystic components of lesions. Imaging techniques, most often fluoroscopy and CT, but also US and more recently open MRI systems, can be used to guide closed biopsy procedures, ensuring accurate needle placement.

Biopsy should only be performed following consultation with the specialized tumor surgeon, and with the pathologist. Success
depends not only on obtaining an adequate tissue sample, but also on the histopathologic interpretation of a relatively small volume of tissue obtained at biopsy.

Angiography is no longer used routinely in the diagnosis and staging of bone tumors, but embolization can be used to reduce the vascularity of a tumor before surgery, or to treat arterial tumor hemorrhage.

**Differential Diagnosis**

Other pathologies may resemble bone tumors, both clinically and radiologically. Infection, in particular, may have radiologically aggressive appearances, with bone destruction or sclerosis, periosteal reaction, and a soft tissue component (Fig. 3-41). Clinical features, such as pyrexia, raised inflammatory markers, and leukocytosis, may favor the diagnosis of osteomyelitis, but biopsy may be needed to confirm the correct diagnosis. It is good practice to include a microbiology sample whenever a bone biopsy of a suspected tumor is performed, to exclude an unexpected diagnosis of infection and avoid unnecessary repeat procedures, should the histopathology prove to be negative. Some metabolic bone disorders (e.g., hyperparathyroidism) are associated with bone cysts or subperiosteal erosions, which can be mistaken for primary bone tumors.

**Imaging Strategies in Soft Tissue Tumors**

Soft tissue tumors commonly present with a mass. In benign tumors, the mass is usually painless and may have been present for months or even years with little change in size. Benign soft tissue masses are 50- to 100-fold more common than sarcomas. Soft tissue lesions caused by trauma (myositis ossificans) (Fig. 3-42) and infection must be differentiated from tumors.

The role of imaging in soft tissue masses is to

- Confirm the presence of a mass
- Define the tissue composition and nature of a mass—relevant to management, either conservative or surgical
- Identify the anatomic location and extent of the mass—relevant to biopsy site and resectability
- Differentiate between benign and malignant etiologies.

In soft tissue sarcoma, imaging also contributes to

- Local staging
- Identification of metastases
- Assessment of tumor and metastatic response to treatment
- Identification of tumor recurrence.

**Figure 3-40** Follow-up imaging. Magnetic resonance imaging scan of a patient treated previously with an endoprosthesis for osteosarcoma of the proximal femur. Transverse axial T2-weighted image—the recurrent tumor mass has a high signal.

**Figure 3-41** Infection. Osteomyelitis may have features resembling those of bone tumors, and biopsy may be required for definitive diagnosis. A, Acute osteomyelitis of the distal tibia—there is bone destruction in the metaphyseal region, and a periosteal reaction seen as faint calcification in the soft tissue adjacent to the bone cortex was apparent on the film. B, Chronic osteomyelitis of the proximal tibia—there is extensive lysis and sclerosis (sequestrum) extending along the tibial shaft, with consolidated periosteal reaction (involucrum), giving a ‘bone-within-a-bone’ appearance.
Radiographs are usually not helpful in the imaging of soft tissue tumors and may be entirely normal, unless the mass is large, contains fat or calcification, or causes abnormality of adjacent bone. US is a good screening method in the initial assessment of soft tissue masses, particularly those that are small and relatively superficial, providing a simple method of confirming whether a soft tissue abnormality is present. US can indicate whether a mass is cystic, solid, or vascular. US allows assessment of the mass during muscle contraction, and changes in position can be used to define the relationships of a mass to surrounding structures. Confident characterization is possible for certain masses (e.g., neuromas and ganglia). CT can be used to identify soft tissue tumors and define their composition, but the limited contrast resolution of the technique means that interfaces between tumor and normal soft tissue structures can be difficult to delineate. MRI is the modality of choice for characterizing soft tissue tumors: The high-contrast sensitivity makes even small lesions conspicuous (Fig. 3-43). Some benign soft tissue tumors have characteristic appearances on MRI and do not require biopsy or treatment (e.g., lipomas, hemangiomas, cysts, and ganglia) (Fig. 3-44); most have a homogenous signal intensity and show little enhancement with gadolinium-labeled DTPA. The signal intensities on \( T_1 \) and \( T_2 \)-weighted MRI sequences give an indication of tissue composition. Myxomas, cysts, and ganglia show low or intermediate signal on \( T_1 \)-weighted images and higher signal on \( T_2 \)-weighted sequences, whereas lipomas and subacute hematomas are high signal on both \( T_1 \) and \( T_2 \)-weighted sequences. Malignant soft tissue tumors are often large, with irregular, indistinct margins and heterogeneous signal intensity (Fig. 3-45). They usually show prominent patchy enhancement with gadolinium-labeled DTPA, sometimes with cystic or necrotic nonenhancing central components.

FIGURE 3-42  Lateral radiograph of the forearm of a girl who suffered from epilepsy and had a convulsion. Over the next 2 to 4 weeks, a hard mass developed in her arm. There is circumferential calcification in the periphery of a soft tissue mass, lying anterior to the radius and ulna; this is characteristic of traumatic myositis ossificans. It is important to differentiate this lesion from a neoplasm; in a neoplasm, calcification usually lies centrally within the soft tissue mass.

FIGURE 3-43  Magnetic resonance imaging scan. A, Transverse \( T_1 \)-weighted image showing a well-defined soft tissue mass (arrow), which is low to intermediate signal. B, Post gadolinium-labeled diethylene triamine pentaacetic acid showing enhancement following contrast medium. C, Sagittal short tau inversion recovery sequence (fat suppression) shows the tumor to be high in signal, with characteristic ‘tails’ at the proximal and distal ends of the tumor indicative of a neurofibroma.
FIGURE 3-44  A, Lipoma of the thigh. Magnetic resonance imaging scan: coronal T₁-weighted image. B, Transverse T₂-weighted image. The tumor is of uniform signal intensity, similar to that of the normal subcutaneous fat, and showed no enhancement with contrast medium (gadolinium-labeled diethylene triamine pentaacetic acid) (not shown). These are the features of a lipoma.

FIGURE 3-45  Liposarcoma of the left thigh. Magnetic resonance imaging scan: coronal T₁-weighted image (A) and transverse T₂-weighted image (B) confirm a large soft tissue mass with signal characteristics similar to those of subcutaneous fat. However, there are areas of low signal intensity areas within the tumor, suggesting soft tissue components other than fat. C, An inversion recovery sequence in which the fat signal is suppressed shows that a considerable proportion of the tumor tissue components do not suppress, confirming that they are not simply fat. These features indicate a liposarcoma.
Most soft tissue tumors are isointense to muscle on T₁-weighted MRI sequences. Tumors that contain areas of fat, melanin, proteinaceous material, or subacute hemorrhage give a high signal on T₁-weighted images. Calcified or predominantly fibrous tumors give a low signal on all MRI sequences.

Most sarcomas show a high signal on T₂-weighted images because of their increased free water content, as a result of high vascular permeability and edema. However, many soft tissue masses have indeterminate features on MRI scans. All such lesions should be presumed malignant until proven otherwise by pathologic evaluation.

Closed biopsies, with small tumor samples, can give misleading results due to sampling error: soft tissue tumors often show regional variation in grade. As with bone tumors, inappropriately sited biopsies and inadequate marginal resection margins can compromise subsequent effective limb salvage surgery and adversely affect prognosis. Therefore, biopsy, whether open or closed, must be performed only by the experienced surgeon who will perform the definitive surgery, and collaboration between clinician, radiologist, and pathologist is essential.

The staging, prognosis, and management of a tumor are dependent on its size and location, and the presence of lymph node or distant metastases. MRI is the modality of choice for the definition of local tumor extent. Potential resectability depends on the tumor’s location, its relationship to adjacent structures, and whether or not the tumor is limited to a single anatomic compartment. Regional lymph node metastases causing lymphadenopathy may be evident on MRI. The relevant sites of regional lymph node drainage should be included on imaging and scrutinized accordingly, but nodal size is a poor predictor of metastatic involvement.

MRI is also used in the identification of tumor recurrence. Follow-up MRI should be deferred for at least 3 months after surgery to allow postoperative changes to resolve. However, differentiation between tumor recurrence and postoperative fibrosis may be difficult. Paramagnetic contrast agents may help in differentiation, but serial examinations, to assess for change in size, and biopsy may be needed in difficult cases.

A great number of MRI sequences have been developed to potentiate tissue contrast and enhance the conspicuity of pathologic lesions. The high contrast sensitivity of MRI makes it the modality of choice for defining the soft tissue margins of tumors and marrow changes within bones. Therefore, MRI is an important method of imaging to define the extent of tumors.

### Joint Disorders

Abnormalities of joints can occur as a consequence of degenerative, traumatic, or inflammatory arthritis, or be associated with metabolic disorders (e.g., gout or chondrocalcinosis) (Figs. 3-46 and 3-47). In rheumatoid arthritis (RA), an erosive arthropathy with narrowing of the joint space caused by destruction of articular cartilage, is an early feature. Because the affected joints are inflamed and hyperemic, there is soft tissue swelling, particularly at the proximal interphalangeal joints, and periarticular osteopenia. Synovial hypertrophy causes juxta-articular bone destruction (erosions) (Fig. 3-48), most commonly at the metacarpophalangeal and proximal interphalangeal joints. MRI is a more sensitive imaging method than radiography to identify synovial pannus and erosions. Ligamentous damage and laxity cause joint subluxation or even dislocation. In RA, there is little reactive new bone formation, unlike in degenerative joint disease, in which osteophytes and subchondral sclerosis are common features. However, in juvenile RA, bony ankylosis of some affected joints can occur.

Seronegative arthropathies (Reiter’s syndrome and psoriasis) have radiographic features that can closely resemble those of RA but tend not to cause peri-articular osteopenia. These diseases have features that distinguish them from RA; there is usually bilateral (but often asymmetric) sacroiliitis, and there may be associated paraspinal ossification. Reiter’s disease (uveitis, urethritis, arthritis) more commonly involves the lower limbs and is often associated with periosteal reaction (periostitis), and psoriatic arthritis frequently involves the distal interphalangeal joints.
Destruction of articular cartilage, and consequent narrowing of the joint space, is a late feature in degenerative joint disease (osteoarthritis). There is reactive new bone formation causing osteosclerosis and osteophytes (Fig. 3-49). Juxta-articular cysts also occur, and generally have a corticated margin, which is not a radiographic feature of the erosions of RA.

Septic arthropathy is characterized by pain and limited joint movement. An effusion is generally present; US is a useful technique to confirm this feature and can be used to guide joint aspiration, which is usually required to reach a definitive diagnosis. On imaging, there can be peri-articular osteopenia, loss of joint space, synovial thickening, and bone destruction. Rapid reduction in joint space over a short period (2 to 4 weeks) on serial radiographs should always suggest infection as the cause. Similarly, rapid reduction in disc space in the spine suggests an infective etiology. Timely diagnosis and correct therapy are essential in septic arthritis to avoid extensive bone and joint destruction with the clinical consequences that result (pain, deformity, ankylosis, and secondary osteoarthritis). MRI is a sensitive imaging technique for the diagnosis of inflammatory arthritis and the associated soft tissue and bone changes.

When deep pain sensation is disturbed or absent (e.g., in pain asymbolia, neurosyphilis, diabetes), very florid joint destruction can occur (Charcot’s joints) (Fig. 3-50) with complete derangement of the joint, which may be subluxed or dislocated; extensive sclerosis, hyperostosis, bone destruction, and bone fragmentation are generally evident. In the feet of patients with diabetic neuropathy these features may be indistinguishable from osteomyelitis and may coexist.
Response to Injury

Chapter 4

The Effects of Injury and the Inflammatory Response

Jose Trueta y Raspall (1897–1977). Trueta was born and educated in Barcelona, and remained throughout his life a Catalanist patriot. In 1939, he fled from Franco’s Spain and brought his family to England, where his wide experience with war surgery was welcomed. His great interest was the vascular contribution to growth and development; in this field, as well as in that of the renal circulation, he made lasting contributions. For 17 years he held the Nuffield Chair in Orthopaedics at the University of Oxford. His energy and enthusiasm was infectious and nobody who had the privilege to be his student could ever forget him, for he was truly a great man. (From the author’s collection.)

Ilya Ilyich Mechnikov (May 16, 1845–July 16, 1916). Mechnikov believed that certain white blood cells could engulf and destroy harmful bodies such as bacteria. Pasteur scorned the Russian and his theory. Later vindicated, Mechnikov’s work on phagocytes won him the Nobel Prize in 1908.
The publication in 1858 of Virchow’s monumental series of lectures entitled *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre* (The Cellular Basis of Disease and Its Foundations in Physiology and Tissue Pathology), brought a completely new understanding of the fundamental nature of disease, which is still the basic principle underlying medical research. For the first time, it was understood that the cell was the basic unit of the living organism, and that alterations in cell function were responsible for disease states. The study of disease was no longer limited to gross anatomic description. The new pathology depended on the correlation of clinical findings and molecular cell biology.

The basic questions in medicine are: what happens to a cell, and to the tissue of which the cell is a unit after injury, how much injury can the cell sustain, and how does the body deal with the injured cells and effect repair?

### Effects of Injury

#### Degeneration

Degeneration may be defined as ‘A morbid change consisting in a disintegration of tissue or in a substitution of a lower for a higher form of structure.’ Although degeneration resulting from injury is a major topic of this chapter, it is important to bear in mind that injury is not the only cause of degeneration; degeneration is also the end result of *disuse or of getting older*.

Degenerative change is a commonly used term in pathology reports. This is more emotive than substantive. The clinician would be better informed if the report detailed the etiology of and the response to the injury. For example, instead of ‘fragment of degenerated intervertebral disc,’ a more descriptive diagnosis might be ‘fragment of lacerated annulus fibrosus with granulation tissue and early scarring.’

Injury may be physical (mechanical trauma, extremes in temperature, or ionizing radiation), chemical (e.g., the quinolone antibiotics have been associated with rupture of the Achilles and other tendons), or biologic, either intrinsic (metabolic, immunologic, genetic) or extrinsic (bacteria, viruses, fungi, or other organisms). Regardless of the etiology, two effects can be expected: a local effect at the site of injury and a general effect on the body as a whole (e.g., shock following severe hemorrhage in association with an open fracture.)

#### Cellular and Tissue Changes

The cell has a complex structure in which the basic processes of energy conversion, protein synthesis, and other vital activities are constantly taking place (Fig. 4-1). Each cell exists in an ever-changing environment, and its ability to adapt to new conditions determines its continued functional activity. Injury to the cell occurs when conditions in the local environment are such that the cell is unable to maintain its physiologic equilibrium.

The results of injury include altered synthesis (anabolism) or altered breakdown (catabolism), or both. The nature of the injurious agent and the duration of its application determine which process predominates. If only transient alterations occur in the intracellular or extracellular regulatory mechanisms, the cell may revert to its normal basal state when the adverse conditions cease. A more severe yet sublethal injury may result in adaptive changes, recognizable microscopically as hypertrophy, atrophy, or hyperplasia. When the insult is lethal, the necrosis (death) of the cell can be recognized microscopically by loss of staining, disintegration of the nucleus, and breakdown of the cell membranes.

Because of the variability in injurious agents and the widely differing susceptibility of various tissues, it is difficult to generalize about the morphologic effects. However, mechanical injury usually causes cell disruption; freezing depresses cell metabolism and ultimately leads to the formation of destructive intracytoplasmic ice crystals; heat increases rates of metabolism, enzyme inactivation, protein coagulation, and even tissue charring. The effects of ionizing radiation are focused mostly on the nucleus, where it may cause chromosome breakage and gene mutation, leading to neoplasia. Chemicals act both locally and systemically by interfering with metabolic processes in the cell, especially by inactivation of enzymes and denaturation of intracellular protein. Finally, many microorganism manufacture toxins that disturb cell metabolism.

Other considerations also influence the effects of injury: the intensity and duration of application and the site of injury (for example, anoxia rapidly produces irreversible damage to brain cells and cardiac muscle, whereas connective tissue can usually withstand anoxia for considerable periods of time). Last, the effects of injury are influenced by the individual’s general health, including nutritional state, presence or absence of drugs in the body, and so on.

#### Histologic Observations

A fundamental characteristic of living cells is their ability to sense and to adapt to changes in the environment. This ability to adjust enables cells to survive under conditions that might otherwise prove lethal.
Such adaptations, which include atrophy, hypertrophy, and hyperplasia, are commonly observed in many disease processes (Fig. 4-2).

The most commonly observed microscopic change associated with altered cell homeostasis is a change in cell volume. This results from the cell's loss of ability to regulate electrolyte and fluid metabolism, owing to altered function of the mitochondria and the cell membrane. Hypoxia, which affects lipoprotein as well as protein synthesis and secretion, may lead to accumulation of lipid droplets and of amorphous eosinophilic material in both the cell and the extracellular space (Fig. 4-3).

**Atrophy**

Atrophy refers to a decrease in the size and activity of a cell, which occurs as an adaptation to diminished use or as a result of a reduction in blood supply, poor nutrition, or a decrease in normal hormonal stimulation. Cell atrophy is usually accompanied by shrinkage of the affected organ. In parenchymal organs, atrophy may result solely from a decrease in cell size. However, in the later stages of disease the decrease in cell size may also be accompanied by actual loss of cells (Fig. 4-4).

Atrophy in connective tissue is made clinically obvious by changes in the quantity and quality of the extracellular matrix. For example, loss of bone tissue (osteopenia) or loss of cartilage turgor (chondromalacia).

**Hypertrophy**

Hypertrophy refers to an increase in cell size caused by augmentation of the intracellular organelles, especially the endoplasmic reticulum;
as a result, protein synthesis is generally enhanced. Hypertrophy is frequently a compensatory reaction, as in the heart muscles of patients with increased cardiac workload who develop an increased number of myofibrils. In an athlete, not only is there hypertrophy of the skeletal muscle but also a related increase in bone density (Fig. 4-5).

**Hyperplasia**

An example of hyperplasia, an increase in the number of cells, is that commonly seen in the synovium of patients with arthritis. The accelerated breakdown of the joint constituents (cartilage and bone) that occurs in all forms of arthritis leads to enhanced phagocytosis by the synovium. This increased activity is associated with augmentation of the synovial lining cells, thus increasing not only the thickness of the synovial lining but also the absolute area of the synovium, which is frequently thrown up into papillary projections that extend into the joint cavity (Fig. 4-6).

**Necrosis**

Tissue necrosis (death) is a passive process resulting in a breakdown of ordered structure and function following irreversible traumatic damage. Cell necrosis is usually recognized microscopically by changes in the nucleus. These changes include swelling of the nucleus, which is followed by condensation of the nuclear chromatin (pyknosis), and finally by dissolution of the nucleus (karyolysis) (Fig. 4-7).

The gross and microscopic appearance of necrotic cells depends on the organ involved and on the type and extent of injury. In tissue necrosis associated with sudden and complete cessation of the blood supply (an infarct), the affected tissue usually has a loss of translucency, that is, an opaque appearance on gross examination and a firm consistency, like a hard-boiled egg. Microscopic examination of infarcted tissue usually reveals maintenance of structural anatomy, with preservation of the ghost-like outlines of the cells (Fig. 4-8). On the other hand, in most bacterial injuries, the cells are totally broken down, resulting in soft formless tissue in which no structural elements of the cell are recognizable (Fig. 4-9).

In the connective tissue, because the nonviable extracellular matrix is often unchanged cell, necrosis may be easily overlooked. In a bone, the most obvious evidence of cellular necrosis is seen in the marrow, either as fat necrosis and dystrophic calcification or as ghosting of the hematopoietic tissue (Fig. 4-10). On the other hand, changes in the osteocytes may be difficult to recognize (Fig. 4-11), and in general, it can be said that evaluation of the viability of the
osteocytes is a poor way to diagnose bone necrosis. In cartilage, ghosting and sometimes calcification of the chondrocytes is a frequent finding in arthritis (Fig. 4-12). Inflammatory arthritis is often characterized by gross enlargement of the chondrocyte lacunae referred to as Weichselbaum's lacunae, which contain either pyknotic nuclei or no obvious cellular elements (Fig. 4-13).

**Apoptosis**

In addition to the passive cell death following traumatic injury, there is another and fundamentally different form of cell death that is genetically determined. This process balances new cell formation (through the process of mitoses) with programmed cell death (or apoptosis). Apoptosis is actively involved in development and in the continuing lifelong replacement of tissues. Apoptosis also plays a role in some pathologic states including tissue injury in diseases of cellular immunity.

Unlike tissue necrosis, which is generally associated with an obvious inflammatory response, apoptosis is difficult to observe by ordinary microscopic technique, even in very active cellular epithelial linings.

Apoptotic bodies can be recognized in paraffin-embedded sections as small round or oval cytoplasmic masses, which are usually eosinophilic and may contain nuclear fragments. However, the small size of apoptotic bodies together with their short half-life renders them inconspicuous in histologic sections, even if the rate of cell deletion is high (Fig. 4-14). Immunohistologic techniques have been developed that assist in the recognition of apoptotic cells. However, these techniques might be unreliable and it is recommended that a molecular or fluorescence-based assay is used to characterize the extent of apoptosis occurring in a tissue (Fig. 4-15).
Apoptosis has been associated with various orthopaedic pathologies. In rheumatoid arthritis, the hyperplastic synovial lining increases both through enhanced proliferation and inflammatory cell migration, as well as decreased apoptosis.

The chondrocytic production of nitric oxide (NO) and other inflammatory mediators, such as eicosanoids and cytokines, is increased in osteoarthritis. The excessive production of NO may inhibit matrix synthesis and promote the mechanism of cytokine-induced apoptosis of the chondrocytes.

In the postnatal and adult skeleton, apoptosis is integral to physiologic bone turnover, repair, and regeneration. The balance of osteoblast proliferation, differentiation, and apoptosis determines the
size of the osteoblast population at any given time. The osteocytes appear to use some molecular signaling pathways such as the generation of NO and prostaglandins as well as directing cell-cell communication via gap junctions. They may also regulate the removal of damaged or redundant bone through mechanisms linked to their own apoptosis or via the secretion of specialized cellular attachment proteins such as osteopontin.

Certain features of growth cartilage development and mineralization are shared with aging and osteoarthritic cartilage. These include chondrocyte proliferation, hypertrophy, and increased apoptosis. Parathyroid hormone-related protein, one of the central mediators of endochondral development, is also abundant in osteoarthritic cartilage and may play a role in osteophyte formation.

**Calcification**

Dead tissue that does not undergo rapid absorption frequently becomes calcified. This type of calcification, which is not related to a generalized disturbance in calcium homeostasis, is called dystrophic calcification. It is common in areas of infarction, fat necrosis, and also the caseous necrosis of tuberculosis. Of particular interest to orthopaedic surgeons is the calcification commonly found in areas of injured tendons or ligaments (Fig. 4-16).

The association of crystal deposition with senile osteoarthritis is well recognized, and there have been recent advances in understanding the mechanisms whereby calcium crystals may contribute to cartilage damage related to the induction of proto-oncogenes, which, in turn, lead to crystal-induced modulation of normal gene expression in the chondrocytes.

**Injury to the Extracellular Matrix**

The extracellular matrix, which is composed of collagen, proteoglycan (PG), various noncollagenous proteins, and inorganic constituents, is a nonviable material. Nevertheless, it shows the effects of both mechanical, chemical, and enzymatic injury. Fibrillation of the cartilage is an example of mechanical injury with disruption of the collagen framework (Fig. 4-17) and the so-called hyalinization of collagen is caused by chemical (usually enzymatic) breakdown of the fibrillar structure, especially of the intermolecular and possibly the intramolecular cross-linkage of the collagen molecules (Fig. 4-18).

Such injured matrices invariably have altered mechanical properties. The fibrillated cartilage does not function as well as normal cartilage, either in the transmission of load or in providing a low-friction articulating surface. The hyalinized collagen, with its weakened

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**FIGURE 4-16** A. Photomicrograph shows extensive calcification in the capsule of the shoulder joint. Such dystrophic calcification is a common complication of tissue necrosis following injury (H&E, × 10 obj.). B. Focal calcific deposits may result, as in this photomicrograph, in a histiocytic and giant cell reaction (H&E, × 10 obj.).

**FIGURE 4-17** Photograph of the articular surface of a patella, illustrating loss of integrity due to collagen disruption or fibrillation. Around the edge of the patella, there is a striking synovial hyperplasia. The brownish discoloration of the synovium and cartilage is secondary to old hemorrhage.

**FIGURE 4-18** Photomicrograph of fibrous tissue to show loss of most of the nuclei and smudging, or hyalinization, of the collagen matrix (H&E, × 50 obj.).
cross-links, has lost much of its tensile strength. On the other hand, unless structural changes of the bone matrix have occurred, a piece of ‘dead bone’ (i.e., one in which both marrow cells and bone cells are dead), is perhaps as strong as a similar piece of viable bone tissue.

The Inflammatory Response

THE INITIAL PHASE

The inflammatory reaction comprises the collective responses of the body to both local and systemic injury regardless of the injurious agent (i.e., it is not confined to infection). These responses include removal or sequestration of the necrotic tissue and the injurious agents, defense against further injury, and replacement of injured cells with possible restoration of tissue architecture by reparative tissue. Thus, the inflammatory reaction is not confined to the acute, local cellular response, which is a popular misconception; it involves the entire body’s defense mechanism, and it is not completed until a homeostatic state has been restored.

The sequence of events after a limited local injury begins with vascular dilatation and increased blood flow. The blood vessel wall becomes more permeable. White blood cells attach themselves to the vascular endothelium and pass through the wall of the vessel into the extravascular space. These observations, first made in the nineteenth century by Julius Cohnheim, explain Celsus’ four cardinal signs of inflammation:

1. Redness, caused by vasodilatation.
2. Heat, the result of increased blood flow.
3. Swelling, caused by exudation of fluids and cells into the extravascular spaces.
4. Pain, the result of irritation of the local nerve endings.

Swelling, caused by the accumulation of protein-rich fluid (or exudate) in the injured tissue, is always present to a greater or lesser degree during the acute stage of inflammation and occurs because the vessels of the inflamed tissue are directly injured or because they become more permeable.

Increased permeability of the vessels is brought about by substances released from or produced by the damaged tissue. These substances, which are referred to as inflammatory mediators, have two sources: the cells and plasma.

In cells, the mediators are either preformed or are newly synthesized in response to the injurious agent. Preformed mediators include histamine, serotonin (mast cells and basophils), and lysosomal enzymes (leukocytes and monocytes). Newly synthesized mediators are produced principally by leukocytes, monocytes, and endothelial cells and include NO, platelet-activating factor, leukotrienes, prostaglandins, and cytokines. In the plasma, the two primary mediators are the various components of complement and factor XII (Hageman factor).

The complex interactions of these various substances, which affect most aspects of normal physiology as well as pathophysiology, are beyond the scope of this book and are the subject of many monographs.

The accumulation and activation of leukocytes are central events in virtually all forms of inflammation and deficiencies in these processes generally lead to a compromised host reaction. The migration (diapedesis) of leukocytes through the wall of the capillary and venule is an active rather than a passive phenomenon. Even after fluid exudation has passed its peak, leukocyte migration continues, presumably as a result of a persistent chemotactic effect of the injurious agent and the injured tissue (Fig. 4-19).

Although Cohnheim described the migration of white blood cells through the vessel walls, it was Ilya Mechnikov who, a few years later, determined the function of these cells. He observed that they were capable of engulfing foreign matter, including bacteria, and he called this process phagocytosis. Because both large and small cells are involved in phagocytic activity, he called the large cells macrophages and the small cells microphages (now referred to as polymorphonuclear leukocytes [PMNs] or neutrophils) (Fig. 4-20).

The type of cell seen microscopically in the cell infiltrate depends first on the nature of the injury (e.g., bacterial injury results in a marked neutrophilic infiltrate, whereas a mechanical injury does not) and, second, on the elapsed time since injury. Within the first few hours, and up to a day or so, the predominant cells in the tissue exudate are PMNs. However, after a period of 24 to 48 hours, more of the cells in the exudate are seen to be mononuclear—lymphocytes and macrophages. This biphasic response may be the result of a sequential action by specific chemical mediators.

Polymorphonuclear and mononuclear phagocytes migrate into the damaged tissues, where they engulf and digest bacteria and necrotic cells (Fig. 4-21). Phagocytes are equipped for this task by their possession of large numbers of cytoplasmic granules, including...
FIGURE 4-20 Photomicrographs of polymorphonuclear (PMN) leukocytes (A) and histiocytes (B) (H&E, × 100 obj.). (C) Diagrammatic representations of the light microscopic and electron microscopic characteristics of a PMN leukocyte (left) and a histiocyte (right).

FIGURE 4-21 A. This photomicrograph illustrates the events during an acute inflammatory reaction brought on by tissue necrosis (in this case, specifically, by myocardial infarction). A small capillary is congested with blood and with many more PMNs than would normally be expected. These PMNs have infiltrated the vessel wall by diapedesis and are now seen in the perivascular tissue (H&E, × 32 obj.). B. Photomicrograph of an active inflammatory infiltrate surrounding fragmented hyalinized (denatured) collagen (H&E, × 10 obj.).
large dense granules (lysosomes), which contain various enzymes such as acid phosphatase, an antibacterial substance called lysozyme, and peroxidase.

The acute inflammatory reaction may either subside, as is usually the case, or in the presence of continuing cell injury, it may persist and become chronic, which is characteristic of autoimmune diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus) and the introduction of foreign bodies, nowadays especially prosthetic replacements. On microscopic examination, chronic inflammation is distinguished from acute inflammation by a marked increase in the number of mononuclear cells in the inflamed area. These mononuclear cells include macrophages, lymphocytes, and plasma cells (Figs. 4-22 and 4-23). A chronic inflammatory response is also characteristic of certain bacterial infections, including tuberculosis and syphilis, as well as with fungal infection. Most forms of acute and chronic inflammation depend on the recruitment of humoral and cellular components of the immune system.

Immunologically mediated elimination of foreign material requires a number of steps. First, the material to be eliminated (i.e., antigen) is recognized as being foreign. Specific recognition is mediated by immunoglobulins (i.e., antibodies) or by receptors on T lymphocytes that bind to specific determinants (epitopes). Nonspecific recognition (i.e., of denatured proteins or endotoxins) may be mediated by the alternative complement pathway or by phagocytes. The binding of a recognition component of the immune system to an antigen generally initiates production of proinflammatory substances that alter blood flow, increase vascular permeability, augment adherence of circulating leukocytes to vascular endothelium, and promote migration of leukocytes into tissues. The actual destruction of antigens is mediated by phagocytic cells. Such cells may migrate freely (e.g., leukocytes) or may exist in fixed tissue sites as components of the mononuclear phagocyte system (e.g., Kupffer cells in the liver and type A synovial lining cells).

For the most part, the actions of the immune system lead to the elimination of antigens without producing clinically detectable inflammation. The development of clinical chronic inflammation indicates either an unusually large amount of antigen, a virulent antigen, or a depressed immune response.

**The Secondary Phase (Repair)**

The initial phase of the inflammatory reaction serves both as a defense and a means for the removal or sequestration of necrotic tissue; the final component of the inflammatory reaction is repair.

Among the most important mediators of the inflammatory response are the cytokines, which are mostly the product of sensitized lymphocytes and are involved in every stage of wound healing (Fig. 4-24). Some of the factors that affect bone and cartilage growth and repair include transforming growth factor beta, insulin-like growth factor, platelet-derived growth factor, β2-microglobulin, bone morphogenetic protein (BMP), interleukin-1, and tumor necrosis factor.
Eventual restoration of the damaged area may involve cell regeneration of tissue similar to the original, or replacement by fibrous connective tissue (scar tissue); but usually a combination of these two processes occurs. In general, the epithelium of the skin, the gastrointestinal tract, and the respiratory tract, as well as the connective tissues, regenerate well. However, the more specialized and differentiated tissues are, the more limited their regenerative capacity. It is important to recognize that cellular regeneration does not imply restoration of anatomy, and in the case of the connective tissues especially, failure to restore anatomy may lead to failure of function.

Perhaps the most characteristic early histologic finding in the reparative stage of the inflammatory response is the proliferation of capillaries and myofibroblasts that comprise granulation tissue (Fig. 4-25). In granulation tissue, the fibroblasts produce the structural extracellular matrix, composed of collagen, PG, and other non-collagenous proteins that give body and strength to the new scar tissue.

The clinician should take every opportunity to promote regulated healing and prevent both delayed healing and excessive scarring. Therapeutic measures include wound débridement, adequate administration of antibiotics, use of nonreactive suture material, and good surgical technique. The avoidance or at least the limitation of drugs that suppress the inflammatory reaction (e.g., cortisone and nonsteroidal anti-inflammatory drugs) is important, and adequate intake of substances necessary for wound healing (protein and vitamin C) is essential.

During most of the inflammatory response, the exudative and reparative events take place simultaneously, although the exudative features predominate in the early stages of the process, and the reparative aspects become more prominent after the removal or neutralization of injurious agents and the removal of necrotic tissue by the macrophages.

Following is a series of discussions on repair of connective tissues after trauma.

**Surgical Wound Healing**

In the case of a surgical wound, all the tissue in the path of the knife blade (including epithelium, fibrous connective tissues, blood vessels, nerves, and fat) is injured either reversibly or irreversibly. When the wound edges have been apposed and sutures applied, a thin clot fills the space between the apposed wound edges and, in the absence of bacterial contamination, the acute inflammatory response is limited. The macrophages rapidly mobilize to remove red blood cells, fibrin, and damaged tissue. Meanwhile, myofibroblasts on either side of the wound hypertrophy and migrate, together with capillary sprouts, and within a few days, circulation is re-established across the margins of the wound.

As the myofibroblasts lay down collagen, the cellular inflammatory infiltrate diminishes. The epithelial cells at the surface begin to undergo mitosis and to migrate over the vascularized granulation tissue. In the case of a nonlinear wound, as the epithelial cells migrate over the granulation tissue, they extend beneath the fibrin clot (scab) that closes off the surface of the wound. When the epithelium is firmly re-established underneath the scab, the scab sloughs (Fig. 4-26).

The suture material used to appose the wound edges frequently causes a foreign body giant cell reaction. In our experience, this has been most severe with some types of absorbable sutures in which the suture material breaks up into myriads of fragments (Fig. 4-27). The suture may also act as a track along which bacteria may travel. If infection occurs, healing is delayed until the infection has been overcome. Healing may also be delayed if there is poor circulation in the area or if the patient is severely debilitated.

**Muscles**

Contrary to widespread belief, muscle tissue regenerates well, but the restoration of normal structure and function is very dependent on the type of injury sustained.

In severe infections, muscle fibers may be extensively destroyed. However, the sarcolemmal sheaths usually remain intact and rapid regeneration of muscle cells within the sheaths occurs, so that the function of the muscle may be completely restored (Fig. 4-28). After the transection of a muscle, muscle fibers may regenerate either by growth from undamaged stumps or by growth of new, independent fibers. The nuclei for both of these processes are derived from the satellite or reserve cells found in the endomysium. However, as the muscle fibers regenerate and grow, there is also an ingrowth into the damaged muscle of capillaries and fibroblasts, with accompanying production of collagen; this scarring usually overrides and prevents muscle fiber regeneration (Fig. 4-29). In cases of trauma, muscle regeneration and healing greatly depends on the correct alignment of the supportive structures by meticulous surgical restoration. Functional restoration also depends on the ability of existing nerve fibers to reinnervate regenerating myofibers.

![Figure 4-25](image-url) A. Photomicrograph of a section through ulcerated skin showing granulation tissue and chronic inflammation (H&E, × 4 obj.). B. Photomicrograph of granulation tissue in an early stage of repair. Note the fibrin clot on the left, and the proliferating fibroblasts and capillaries interpersed with chronic inflammatory cells toward the right (H&E, × 10 obj.).
Compartment syndrome, that is, swelling and ultimate loss of viability of a muscle group, is caused by compromised circulation within a confined anatomic space. The condition most commonly involves the anterior tibial compartment of the leg, the volar compartment of the forearm, or the interosseous compartments of the hand (Fig. 4-30).

In general, compartment syndrome results from trauma to an extremity (usually a fracture or crush injury; recently, the disorder has also been seen in patients suffering from intravenous drug overdose). Vascular occlusion from either direct injury or increased pressure within the anatomic compartment leads to diminished tissue viability and function. Pain and swelling are prominent symptoms. Muscle necrosis ensues, and eventually the original tissue is replaced by dense, fibrous connective tissue, with subsequent deformity and loss of function. Microscopic findings depend on the stage at which the tissue is obtained. Muscle necrosis, granulation, scar tissue, and calcification may be present (Fig. 4-31).
CHAPTER 4 THE EFFECTS OF INJURY AND THE INFLAMMATORY RESPONSE

**Figure 4-29** Photomicrograph of damaged myocardial tissue shows extensive fibrous scarring, with only a few muscle fibers enmeshed in the dense scar tissue. This scarring blocks any potential for regeneration and restoration of the muscle tissue (H&E, × 25 obj.).

**Figure 4-30** A. Clinical photograph of the arm in an untreated patient who developed compartment syndrome after multiple injuries to the elbow and forearm some months earlier. Note the severe flexion contractures. B. Radiograph of the arm shown in A. In addition to evidence of traumatic arthritis, there is also immature bone formation around the ulna and radius in the upper third of the forearm. C. Photomicrograph shows that the involved soft tissue is entirely necrotic. The purple-stained areas have calcified (H&E, × 4 obj.).
Treatment of the acute condition is aimed at relieving the pressure by fasciotomy, the removal of tight bandages, or whatever is appropriate to the circumstances.

**Tendons and Ligaments**

Traumatic rupture of a tendon or ligament in a healthy individual is rare, occurring only in association with a severe injury or with chronic repetitive injury. The slow application of excessive load usually results in an avulsion of the tendinous or ligamentous insertion and includes the bone. The rapid application of excessive load in a tendon usually results in a separation at the musculotendinous junction. Risk factors for spontaneous (i.e., low threshold) rupture include fluoroquinolone or steroid therapy; hypercholesterolemia; rheumatoid arthritis; Marfan’s syndrome, Ehlers-Danlos syndrome, and other connective tissue diseases.

Tendons may heal either as a result of proliferation of the tenoblasts from the cut ends of the tendon, or more likely, as a result of vascular ingrowth and proliferation of fibroblasts derived from the surrounding tissues that were injured at the same time as the tendon (Figs. 4-32 and 4-33). Because the surrounding tissues contribute so much to the healing of a tendon, adhesions are very common. To avoid this complication, the repair of lacerated tendons in the hand requires meticulous atraumatic technique. With rupture of the Achilles tendon or of the cruciate ligament, functional restoration usually requires apposition and suturing of the cut ends.

**Peripheral Nerves**

When a nerve fiber is divided, the peripheral portion rapidly undergoes myelin degeneration and axonal fragmentation. The lipid debris is removed by macrophages mobilized from the surrounding...
tissues (wallerian degeneration). In the central stump, the nerve fibers retract and the axons adjacent to the cut degenerate. However, within 24 hours of section, new axonal sprouts from the central stump can usually be demonstrated, together with proliferation of Schwann cells from both the central and peripheral stumps (Fig. 4-34). With careful microsurgical approximation of the nerve, reinnervation may be achieved. The most important requirement of successful nerve regeneration following repair is the maintenance of the neurotubules along which the new axonal sprouts can pass.

CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome is an entrapment neuropathy caused by pressure on the median nerve as it passes under the transverse carpal ligament and over the hollow of the carpal bones (Fig. 4-35). Patients usually report night pain, often accompanied by paresthesia in the distribution of the median nerve. In advanced cases, wasting of the thenar muscles may occur. The cause of the increased pressure varies, but most often it results from post-traumatic fibrosis or synovitis. Occasionally carpal tunnel syndrome may herald rheumatoid arthritis or other synovial disease and, on rare occasions, it has been found to result from amyloid deposits (a discussion on the difficulties of diagnosing amyloid in connective tissue is found in Chapter 9).

The condition is treated by surgical division of the transverse carpal ligament. At operation, the nerve is often seen to be congested above the ligament, and constricted and pale where it lies under the ligament (Fig. 4-36).

Microscopic examination of the transverse carpal ligament usually reveals nonspecific fibrosis and occasional fibrocartilaginous metaplasia. Two conditions that may be related to carpal tunnel syndrome are trigger finger and de Quervain’s disease (stenosing tenovaginitis of the common tendon sheath of the abductor pollicis longus and the extensor pollicis brevis). In both of these conditions,
Section II  Response to Injury

the free movement of the tendon is blocked by a focal thickening of the tendon sheath, which results from fibrocartilaginous metaplasia (Fig. 4-37). The treatment is excision.

Bone

Fracture

Fracture of the bone results from a combination of mechanical injury, failure of neuromuscular coordination (unsteadiness), and the strength of the bone itself. Many fractures seen in hospital practice are in elderly people. In these patients, fractures of the vertebral bodies, femoral neck, and wrist are common, usually as the result of osteoporosis, together with an increased liability to falls resulting from a deterioration in neuromuscular coordination. A recently recognized fracture mostly seen in elderly individuals is a subchondral insufficiency fracture usually occurring in the femoral head or in the medial femoral condyle of the knee (Fig. 4-38). These lesions are discussed in more detail in Chapter 11. Children with meningomyelocele may present with severe periarticular fractures in the lower limb resulting in a Charcot’s joint, which may on occasion simulate a malignant tumor (Fig. 4-39).

Child abuse and even abuse of the elderly often lead to nonaccidental traumatic fractures. These fractures may be present without there necessarily being any external evidence of trauma. In children, such fractures need to be distinguished from pathologic fracture secondary to an underlying metabolic disturbance such as osteogenesis imperfecta.

Pathologic fractures result from weakening of the bone caused by local disease such as tumor or infection. In such a case, the underlying disease process may be masked by the fracture callus and therefore not readily be apparent to the attending physician.
The minor injuries of everyday life may result in individual trabecular fractures or microfractures (Figs. 4-40 and 4-41). Repetitive stress to the bone, as occurs in hikers, long-distance runners, and very commonly in dancers, may result in cumulative microfractures and the development of stress (or fatigue) fractures usually in the feet or in the tibia (shin splints) (Figs. 4-42 and 4-43). Such lesions occur without a history of significant mechanical trauma, and therefore may be misinterpreted by the clinician, radiologist, or pathologist as a neoplasm.

Repeated trauma at ligamentous and tendinous insertions that results in an avulsion fracture may also exhibit a pseudosarcomatous appearance, both radiographically and histologically. In young adolescents, such injuries are most likely to occur in and around the pelvis, particularly at the origins of the adductor muscles along the inferior pubic ramus adjacent to the symphysis pubis, the lower head of the rectus femoris just above the acetabulum, and the origins of the hamstring muscles at the ischial tuberosity, as well as the insertions of the gluteus at the greater trochanter and the psoas at the lesser trochanter (Fig. 4-44). Repeated trauma at the insertion of the adductor muscles of the thigh may lead to the formation of a bony spur on the lower medial aspect of the femur, often referred to as a rider’s spur because it is commonly seen in those who ride horseback. In children around...
Section II
RESPONSE TO INJURY

Response to Injury

The ages of 10 and 11 years, avulsion fractures are also seen at the tibial tubercle, where the effects of the injury and eventual repair result in the lesion known as Osgood-Schlatter disease (Fig. 4-45).

Because bone is a composite material and is also anisotropic (see Chapter 1), the gross appearance of a fracture depends on the microstructure of the bone tissue. Bone’s most important structural features in terms of fracture propagation are its many weak interfaces, which include both the cement lines as well as the osteocyte lacunae and canaliculi dispersed throughout the matrix. The osteocyte lacunae can act as sites of crack initiation, and the cement lines provide the major planes of fracture propagation (Fig. 4-46). The alignment of the cement lines in the cortical bone is predominantly longitudinal and is partially responsible for the obliquity of most fractures in the shafts of long bones. In diseases in which the microstructure of bone is markedly disturbed (e.g., in osteopetrosis or Paget’s disease), the transverse pattern of fractures in a long bone reflect the disturbance in micro architecture.

The direction in which a load is applied also determines the direction of the fracture. In general, tensile loads cause flat fractures, whereas compressive loads result in oblique fractures, usually with greater damage to the bone. Bending forces cause fractures that combine the features of tensile and compressive fractures, and torsional loads usually lead to helical fractures (Fig. 4-47).

Bone Fracture Repair

Fortunately, the healing of bone is one of the great successes of nature. Under favorable conditions and provided the fractured ends are properly aligned, bone can regenerate and remodel to function optimally.

The single most important factor in the primary healing of a fracture is complete immobilization of the fractured bone ends. In nature, this immobilization is achieved through the production of

**Figure 4-42** In this young individual (open growth plate), an area of sclerosis is apparent on the medial side of the tibia. Overlying the sclerotic area is a periosteal reaction extending down the shaft of the tibia. A horizontal lucent line in the sclerotic zone marks the fracture line.

**Figure 4-43** Clinical radiograph of a stress fracture of the leg. A patient with this type of fracture usually does not have a history of trauma, and presents clinically with pain and swelling in the affected parts after strenuous physical activity. The periosteal elevation, combined with a lack of displacement or obvious fracture line through the bone, may lead to this fracture being misdiagnosed radiographically as a tumor. Even if a biopsy is obtained, the hypercellular appearance of the callus may lead the pathologist to believe that this is a cellular bone-forming neoplasm or, as in this case, an osteoid osteoma.

**Figure 4-44** Clinical radiograph shows an avulsion fracture in the pelvis. Note the fragmentation due to avulsion injury of the ischial tuberosity. This fracture, like the stress fracture in Figure 4-43, may easily be misdiagnosed as a tumor, either radiographically or microscopically.
Chapter 4

The Effects of Injury and the Inflammatory Response

Immature bone and cartilage matrix by the cambial layer of cells in the periosteum and from undifferentiated mesenchymal cells in the soft tissues around the broken ends of the bone (Fig. 4-48). This immature reparative tissue is referred to as the fracture callus (Fig. 4-49).

The amount of callus produced depends on a number of factors, including the degree of instability and the vascularity of the injured bone. The amount of callus is increased in unstable fractures, and usually contains much cartilage tissue (Fig. 4-50). In poorly vascularized areas of the skeleton (e.g., the midshaft of the tibia), callus formation may be scant; consequently, healing may be delayed, sometimes indefinitely, thus resulting in chronic nonunion at the fracture site (Fig. 4-51).

When a fracture occurs, the amount of injury sustained by the bone itself and by the surrounding soft tissues depends on the direction and magnitude of the force applied. The bone fragments may be displaced. The fracture line may be single (a simple fracture) or the bone may be broken into many fragments (a comminuted fracture). If the skin over the fractured bone is also broken, the injury is considered to be a compound fracture, and infection is a common complication. In some cases, soft tissue may become interposed between the fractured ends of the bone, causing healing to be significantly delayed. For all these reasons, the histologic appearance of the reparative tissue surrounding a fracture is extremely variable.

Tissue obtained within a few days of injury usually shows areas of hemorrhage and acute tissue damage (Fig. 4-52). The bone and bone marrow on either side of the fracture undergo necrosis, the extent of which depends on the local anatomy (Fig. 4-53). Fractures of the femoral neck, some of the carpal and tarsal bones, and the patella frequently demonstrate widespread bone necrosis because the local vascular supply is severely compromised (Fig. 4-54). In a comminuted fracture, the separate bone fragments are also likely to undergo necrosis. If bone or soft-tissue necrosis is extensive, healing will be delayed.

Microscopic examination of tissue from a 2-week-old fracture callus generally shows markedly cellular tissue, usually hypervascular, which produces irregular islands and trabeculae of immature bone and cartilage (Figs. 4-55 and 4-56). The hypercellularity and the disordered organization may produce a pseudosarcomatous appearance (Fig. 4-57), and because a biopsy is not likely to be performed unless the clinician has failed to recognize the traumatic origin of the patient’s complaints, the pseudosarcomatous appearance of the callus can easily lead to errors in interpretation by the pathologist. It cannot be too strongly emphasized that because stress fractures without an obvious history of injury are common in young people (the same age group as osteosarcomas), clinical recognition of the

**Figure 4-45** Clinical radiograph of the knee in a 12-year-old child shows fragmentation and avulsion of the tibial tubercle. This condition, known as Osgood-Schlatter disease, is almost certainly post-traumatic.

**Figure 4-46** As bone fracture develops, the propagation of cracks is likely to follow the cement lines. In this photomicrograph, the cement lines are indicated by cracks that have developed during tissue sectioning (H&E, × 10 obj.).
Section II: Response to Injury

The true nature of the problem is important and, on occasion, is among the most difficult problems in differential diagnosis (Fig. 4-58).

Once the callus is sufficient to immobilize the fracture site, repair occurs between the fractured cortical and medullary bones. When union has been achieved, the callus is remodeled and eventually disappears.

Very little callus is produced when a fracture is treated with rigid internal or external surgical fixation, where primary healing of the bone proceeds without the abundant external callus seen in association with unstable fractures.

Many factors influence the repair of a fracture. These include the particular bone involved (the tibia being especially difficult), the portion of the bone involved (the diaphysis is worse than the metaphysis), the type of fracture (comminuted versus simple), the degree of soft tissue injury, interposition of soft tissue between the fractured bone ends, and the stability of the site after fixation. Evaluation of fracture repair in any clinical study must consider the effects of these factors. When there is nonunion of a previous fracture

Figure 4-47 These diagrams illustrate three different kinds of fractures, and how they are caused. **Left**, Transverse fracture, caused by traction (pulling force). **Center**, Oblique fracture caused by compression. **Right**, Helical fracture, caused by torsion. These differences in the pattern of fracture apply not only to a whole bone but to an individual trabeculum.

Figure 4-48 Low-power photomicrograph shows reparative new bone that has formed in the soft tissue and periosteum surrounding a fractured rib. Restoration of bone cortex and medulla depends on complete immobilization of the fracture site, which is accomplished naturally through the formation of external callus. (However, when a fracture is treated by rigid internal fixation, external callus may not be evident, because it is not necessary.) (H&E, × 1.5 obj.)

Figure 4-49 Fine grain radiograph to show the fine trabecular pattern of callus (**left**) as compared with normal cancellous bone (**right**) (magnification × 4).
or when large bone defects are present, grafting with autografts (from another anatomic site in the same patient), allografts (from other human subjects), or xenografts (from animals) is an accepted practice (Fig. 4-59).

Histologic evidence from experimental studies of fracture repair and ectopic ossification indicates the necessity of a rigid calcified framework for lamellar bone to be deposited. The composition of this framework may be calcified cartilage, calcified woven bone, or
even foci of dystrophic calcification. When such a framework exists and lamellar bone is produced, it is said to be osteoconductive, playing the role of a filler to assist in the bridging of a gap (usually a fracture line). Most bone grafts act in this way (Fig. 4-60); however, it has been shown that certain proteins (BMPs) derived from bone and bone marrow are osteoinductive, that is, they stimulate the formation of bone matrix by the cell. A mixture of bone graft (osteoconductive) and admixed bone marrow BMP (osteoin-ductive) will work better as a graft than a bone graft alone.

Fractures may also lead to systemic complications, including shock syndrome and myoglobinuria, the latter occurring when there is significant muscle injury. Associated with all fractures is a disruption of the bone marrow, with the potential for embo-lization of the fatty marrow through the locally damaged venous system. Fat embolization becomes a clinical problem in severe multiple fractures and extensive orthopedic surgery, for example, bilateral joint replacements, and may result in petechial hemorrhages, cerebral ischemia, or pulmonary insufficiency (Fig. 4-61). The effects of fat emboli on the tissues are, first, mechanical obstruction of the capillary bed and, second, an inflammatory response resulting from breakdown of the fat into free fatty acids.

**CONGENITAL PSEUDOARTHROSES**

A pseudoarthrosis (false joint) usually occurs in adult life as a complication of a fracture. However, it may also manifest at birth or during infancy, commonly in the shaft of the tibia (or rarely the ulna). The lesion is usually observed at the level of the junction of the middle and lower third of the bone shaft. This type of pseudoarthrosis is considered congenital and constitutes a distinct orthopaedic entity.

Radiographic evaluation of an infant with congenital pseudoarthrosis reveals discontinuity in the diaphysis of the affected bone,
associated with a characteristic tapering of the bone ends at the site of the pseudoarthrosis (Fig. 4-62). Histologic examination reveals dense, fibrous connective tissue filling the defect (Fig. 4-63).

Neurofibromatosis is present in a high percentage of children with this condition, and as many as 10% of patients with neurofibromatosis have the disorder. Nevertheless, neurofibromas are not usually recognized on microscopic examination of histologic specimens from the involved site. These lesions usually prove to be very refractory to treatment.

**Cartilage**

Healing of cartilage is adversely affected by three factors: its avascularity, its low cell-to-matrix ratio, and its interstitial pattern of growth, in contrast to the appositional growth of bone. Nevertheless, it is essential to recognize that cartilage cells can indeed proliferate, and that in arthritis, in which the cartilage is damaged, cartilage regeneration with both cartilage cell proliferation (Figs. 4-64 and 4-65) and cartilage matrix production is a regular feature. Similar processes also occur at the borders of a traumatic cartilaginous defect (Figs. 4-66 to 4-68).

The ability of cartilage cells to produce an adequate matrix and to restore functional tissue probably depends on their mechanical...
environment. After an injury to the articular surface, as might occur in an athletic injury, continued use and irritation will probably result in worsening of the condition. (Cartilage repair is discussed at greater length in Chapter 10.)

Menisci of the Knee

The menisci are composed mainly of collagen, although some PG is also present. The amount of PG increased dramatically in the injured meniscus and is associated histologically with cartilaginous metaplasia in the injured tissue. Examination of carefully oriented sections has revealed that the principal orientation of the collagen fibers in the menisci is circumferential (see Fig. 1-63). The few small, radially disposed fibers that do occur exist primarily on the tibial surface. The circumferential orientation of most of the collagen fibers is designed to withstand the circumferential tension within the meniscus during normal loading. The radially disposed fibers probably act as ties to resist longitudinal splitting of the menisci that might result from undue compression.

FIGURE 4-60 Photomicrograph of tissue obtained from an area previously grafted with bone tissue broken into very small pieces. New bone has formed and surrounds the fragments of grafted bone (H&E, × 4 obj.).

FIGURE 4-61 Photomicrograph of lung tissue showing globules of fat in the alveolar walls (frozen section; oil red O stain, × 4 obj.).

FIGURE 4-62 A, Anteroposterior radiograph of a young boy with congenital pseudoarthrosis of the tibia and fibula. The appearance of the lesion at the junction of the middle and lower third of the bones and the tapering of the bone ends are characteristically found in patients with congenital pseudoarthrosis. B, Lateral radiograph of the case shown in A.
The menisci of young individuals are usually white, have a translucent quality, and are supple on palpation. The menisci in older individuals lose their translucency, become more opaque and yellow in color, and feel less supple (see Fig. 1-55).

Lacerations of the meniscus cause symptoms that require surgical treatment in two groups of patients: young active patients in whom injury is frequently related to athletic activity, and older individuals in whom degeneration leads to laceration. In older individuals a good deal of fraying of the inner edge of the menisci is a frequent occurrence. Most significant lacerations take place in the posterior horn of the meniscus and, more commonly, in the medial meniscus. They usually occur as clefts that run along the circumferentially directed collagen fibers (Fig. 4-69). Extension of the tear may lead to the bucket-handle deformity (Fig. 4-70). Over time, such a cleft may extend to the medial margin of the meniscus and create a tag, which eventually may become quite smooth (Fig. 4-71). Sometimes, the
The meniscus shows peripheral detachment, again usually posteriorly. Fraying of the inner margin of the meniscus is found at autopsy in over 50% of older individuals (Fig. 4-72).

The development of arthrography, and later magnetic resonance imaging and arthroscopy, has greatly improved the clinical diagnosis of tears in the menisci. These techniques help to localize tears and, when the scope of the injury is limited, can facilitate partial meniscectomy.

In histologic sections of torn menisci, evidence of both injury and repair may be seen, with the findings likely to be time dependent (Fig. 4-73). In sections of a torn meniscus, it is not unusual to see cartilaginous metaplasia, probably resulting from the altered loading pattern (Fig. 4-74). However, it is difficult to determine whether histologic degenerative changes observed at meniscectomy result from or contribute to the tear (Fig. 4-75).

**Synovium**

Injury to any of the joint structures necessarily affects the synovium. Traumatic synovitis is usually characterized microscopically by evidence of hemorrhage (hemosiderin staining), hypertrophy and
Occasionally, a tear as shown in Figure 4-69 will extend onto the medial margin and form a tag that extends into the joint space. Such a tag may become smooth at its margins, as seen in this specimen.

The lateral meniscus removed from an older individual. Notice the yellow discoloration; fraying of the inner margin is present, together with some small clefts.

Photomicrograph to demonstrate cartilaginous metaplasia within injured meniscal tissue. This alteration is probably the result of local alterations in loading from predominantly tensile to predominantly compressive (H&E, × 40 obj.).

Photomicrograph of meniscal tissue shows foci of normal-appearing collagen at the upper left; collagen fibers, which are frayed, in the middle; and myxomatous tissue, possibly the result of degenerative changes, at lower right (H&E, × 25 obj.).
hyperplasia of the synovial lining cells, mild chronic inflammation, and occasionally by included fragments of detached bone and cartilage (Fig. 4-76). Sometimes the severity of the synovial response may obscure the underlying traumatic etiology and lead to a mistaken diagnosis of pigmented villonodular synovitis (Fig. 4-77).

**Summary**

Mechanical trauma is a major cause of skeletal malfunction. Trauma also plays a contributory role in a number of other morbid conditions, including but not limited to osteoarthritis, slipped capital femoral epiphysis, myositis ossificans, and interdigital (Morton’s) neuroma of the foot, all of which are discussed in greater detail later.

The response to injury (the inflammatory response) is effected mainly locally and through the vascular system; its purpose is to restore the body to its status quo. In the case of minor injuries that frequently befall all of us, the status quo is indeed restored. In the case of more severe injury, however, a new status quo with resulting disability is more likely to occur. Effective management of such disabilities is dependent on a thorough understanding of pathogenesis.
Bone and Joint Infection

Pyogenic Infections and Other Nongranulomatous Inflammatory Conditions, 110

- Clinical Considerations, 110
- Radiographic Diagnosis, 120
- Bacteriologic Diagnosis, 122
- Morbid Anatomy of Osteomyelitis, 122

Granulomatous Inflammation of Bones and Joints, 127

- Mycobacterial Infection (Tuberculosis), 127
- Atypical Mycobacterial Disease, 130
- Sarcoidosis, 132
- Mycotic Infections, 133
- Parasitic Infections, 134
Because it is so common, the physician understandably thinks first of infection when signs of inflammation are present; however, it is very important to remember that inflammation also occurs in response to other pathologic processes, including trauma, immunologically mediated disease (e.g., rheumatoid arthritis), some metabolic diseases (e.g., gout), and even neoplasia.

It was only in the late 19th century that the clinical picture of bone marrow infection (osteomyelitis) became recognized for what it is. Before the era of antibiotics, bone and joint infections were both common and serious clinical problems resulting in high rates of morbidity and mortality. In the present day, the incidence of osteomyelitis and its associated mortality has decreased dramatically; however, even with antibiotic use, the morbidity rate remains high. In the third world, bone and joint infections still remain a serious clinical problem.

The prompt diagnosis and management of osteomyelitis depends on a careful correlation of clinical, radiologic, and histopathologic findings. Occasionally, there are problems with differential diagnosis, especially when differentiating osteomyelitis from round cell tumors and eosinophilic granuloma. These problems are encountered not only radiologically and clinically (an Ewing tumor may present with fever and increased sedimentation rate) but also microscopically, especially with small crushed specimens where tumor cells and inflammatory cells may be difficult to distinguish (Figs. 5-1 and 5-2). In such cases, the diagnosis of osteomyelitis may depend on intraoperative cultures in combination with the patient’s subsequent postoperative course; the importance of taking an adequate amount of culture material and its prompt inoculation into the transport medium cannot be overemphasized.

The majority of bone and joint infections are either pyogenic (characterized by neutrophilic infiltration and pus formation) or granulomatous (characterized by multiple nodules or granules in tissue). In general, pyogenic diseases are more common in bone, whereas granulomatous infections are more often found in joints.

**Clinical Considerations**

Infection of skeletal tissue results from microbes that are either blood borne (hematogenous infection) or implanted directly into the bone. The latter is now the most common clinical presentation and most often occurs as a complication of a compound fracture or of surgery.

**Hematogenous Osteomyelitis**

Children comprise the majority of patients with acute hematogenous osteomyelitis. In children older than the age of 1 year, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Haemophilus influenzae* are the most commonly isolated microbes. After 4 years of age, the incidence of osteomyelitis caused by *H. influenzae* decreases in incidence.

The most frequent sites of pediatric osteomyelitis are areas of rapid growth and increased risk of trauma: the distal femur, proximal tibia, proximal femur, proximal humerus, and distal radius (Fig. 5-3). There is some evidence that the large caliber of the metaphyseal veins in children results in a marked slowing of blood flow, predisposing traumatized tissue to thrombosis and subsequent colonization of the area by blood-borne bacteria (Fig. 5-4).

Hematogenous osteomyelitis is uncommon in healthy adults. However, with increased numbers of debilitated individuals (i.e., those with chronic immune deficiency disease or drug addiction), adults with osteomyelitis are being seen with greater frequency. *S. aureus* is the most commonly isolated pathogen in these individuals, although infections with *Staphylococcus epidermidis*, gram-negative rods, and yeasts such as *Candida* are also seen.

Studies of osteomyelitis in intravenous drug users (IDUs) reveal that almost 90% are bacterial in origin with a predominance of pyogenic infections. *S. aureus* and streptococci are the most frequently encountered pathogens. Gram-negative bacilli, particularly *Pseudomonas aeruginosa*, are well known, although less common,
infecting organisms. Polymicrobial infections may occur. Infecting bacteria are carried into the blood from the skin as well as injected from unclean hypodermic needles. Additionally, the injected drugs are often ‘cut’ and thereby contaminated with other particulate matter. The resulting microvascular occlusion provides a ready site for bacterial colonization. Clinical symptoms and signs are often subtle, with fever and chills conspicuously absent in most IDU patients. Local pain may be the sole clinical finding, and thus, the diagnosis of osteomyelitis may be delayed. The focus of osteomyelitis in these patients is usually the spine (Fig. 5-5) or the pelvis, although the disease may occur anywhere in the skeletal system (sometimes in unusual sites such as the clavicle). When long bones are involved, radiographic changes include lyases of affected bone as well as sclerosis and periosteal reaction (sometimes in an onion skin pattern), which may result in a misleading diagnosis of malignancy.

In elderly individuals, especially those with genitourinary infections, opportunistic bacteria selected out by repeated antibiotic use, usually *P. aeruginosa*, gain access to the spine possibly via Batson’s venous plexus (Fig. 5-6). Another group of elderly patients in whom

**FIGURE 5-3** Distribution of osteomyelitis in children and adults.

**FIGURE 5-4** After mechanical trauma to the bone in children, the large venous channels in the metaphysis are liable to thrombose (see vein on right). In the presence of bacteria from infection elsewhere in the body, such a site of thrombosis can act as a nidus for bacterial growth and subsequent development of osteomyelitis.

**FIGURE 5-5** Radiograph of a lateral portion of the spine in a young drug addict. There is narrowing of the disc space T12–L1 and bone sclerosis anteriorly on both sides of the disc between L2 and L3 and extensive destruction at L4–L5 and L5–S1, with collapse of L5. Bacteriologic culture showed that the offending organism in this case was *Staphylococcus aureus*. 
Osteomyelitis may be a problem are those with peripheral vascular insufficiency, which in many cases is associated with diabetes. In these patients, the infection usually involves the small bones of the feet. The etiology is frequently polymicrobial; likely suspects include *S. aureus*, *Streptococcus agalactiae* (group B streptococci), *Enterococcus* (group D streptococci), and gram-negative bacteria as well as anaerobic gram-positive cocci.

Adults with bone infections often present only with pain; thus, a diagnosis of osteomyelitis may not be obvious. As already mentioned, the accompanying radiographic bone changes are easily misinterpreted by the radiologist as a malignant tumor (Fig. 5-7). The clinical diagnosis may be further confused by negative cultures resulting from inappropriate empirical use of antibiotics.

**Neonatal Osteomyelitis**

Neonatal osteomyelitis commonly involves the joint adjacent to the involved bone, and is usually the result of hematogenous infection by one of three organisms: *S. aureus*, *S. agalactiae*, or *Escherichia coli*. *S. agalactiae* is commonly found in the vagina, and the unborn child presumably becomes infected during delivery. *E. coli*, a common contaminant at the time of delivery, can become pathogenic in neonates because of the infant’s immature immune system.

In the case of *S. aureus* and *E. coli* infections, about 40% of the neonatal patients show polyostotic involvement (Fig. 5-8) (polyostotic involvement with osteomyelitis is extremely rare except in...
the neonate). When *Streptococcus* is the causative organism, usually only a single bone is involved. In some cases of neonatal osteomyelitis, the absence of systemic symptoms (because of immunologic incompetence) can delay the clinical diagnosis.

**Osteomyelitis Resulting from Direct Inoculation of Bacteria**

Today, acute hematogenous osteomyelitis of childhood, which used to be regularly seen in orthopaedic practice, is much less frequent; post-traumatic osteomyelitis has become a more common clinical problem. Post-traumatic osteomyelitis usually results from puncture wounds, traffic accidents, and surgery (Figs. 5-9 and 5-10).

Most traffic accidents involve high-impact collisions causing compound and comminuted fractures. A significant amount of foreign material, including metallic debris, pieces of clothing, or soil, is usually found in these wounds. It is important to recognize the polymicrobial nature of the infection in accident cases. *Staphylococcus* and *Streptococcus* infection can be expected; in addition, gram-negative organisms (including *Pseudomonas*) are often present. The most important first step when treating these patients is removal of all foreign and dead matter. If this step is omitted, elimination of the infection becomes difficult, if not impossible. Potent, preferably targeted, antibiotic treatment should be administered for as short a period as possible. (Antibiotic selection should reflect local susceptibility patterns.)

When osteomyelitis is a complication of a fracture, it is important to completely immobilize the fracture fragments because without immobilization, it is virtually impossible to re-establish the vascular supply necessary to adequately deal with the infected and inflamed tissues (Fig. 5-11).

Iatrogenic infections may be a direct result of surgical intervention, associated with internal fixation of a simple or compound fracture, or with prosthetic joint replacement. (More than 500,000 prosthetic joint replacements are performed each year in the United States alone.) After a total joint replacement procedure, infection may occur as an acute complication of the operation or may present insidiously many months (or even years) later (Fig. 5-12). The causative organisms commonly identified in such

![Figure 5-9](image1.png) Radiograph of the left thumb of a 15-year-old boy with recent swelling of the first metacarpal following a penetrating injury. The radiograph shows patchy sclerosis and mature periosteal bone formation secondary to infection. (Courtesy of Dr. Alex Norman.)

![Figure 5-10](image2.png) Radiograph of the right knee of a 13-year-old boy with a recent history of pain and stiffness in the knee following a fall in which the skin was punctured. The lytic area within the otherwise dense femoral epiphysis proved at biopsy to be an abscess. (Courtesy of Dr. Alex Norman.)

![Figure 5-11](image3.png) Photograph of a tibia amputated for an infected nonunion of a compound fracture of the mid-diaphysis.
cases are *Staphylococcus* (both coagulase negative and coagulase positive), gram-negative organisms such as *Pseudomonas* species or *E. coli*, and a variety of anaerobic organisms may also be found. Improved surgical technique and the use of hood, suit, and laminar flow have dramatically reduced the incidence of infection to less than 0.5% for both hips and knees in some institutions. (A further discussion of infection associated with total joint replacement is found in Chapter 14.)

We have seen a few cases of secondary infection following arthroscopy, and in two of these cases, the organism was a fungus (one candida) and the other cryptococcus. In rare cases actinomycosis (*Actinomyces israeli*) may gain access to the bone through a puncture wound, and such a case is illustrated in Figures 5-13 and 5-14.

**Chronic Osteomyelitis**

With the mortality rate reduced to almost zero, few people die from hematogenous osteomyelitis; however, between 15% and 30% of patients go on to develop chronic disease. Chronic osteomyelitis is frequently the result of either inadequate antibiotic treatment or incomplete surgical débridement of necrotic bone. Necrotic bone within the affected area (the sequestrum) protects bacteria from even high levels of appropriate antibiotics. Furthermore, recent data implicate bacterial bio films—the formation of sessile microbial communities with inherent resistance to antimicrobial agents—in the genesis of chronic osteomyelitis. Occasionally, bio films developing on dead tissue such as the sequestra of dead bone give rise to nonsessile colonies that may multiply rapidly and disperse. The biofilm acts as a nidus of infection, and acute disease results when host defenses cannot eliminate the released bacteria. Bio films associated with osteomyelitis are usually composed of a mixture of various bacterial and fungal species, and the disease is not resolved until the sessile population is surgically removed.

Indeed, it has been known for a long time that *Staphylococcus* species of the same phage type as the original infecting bacteria have been isolated from patients with relapsing osteomyelitis years after the initial infection.

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**Figure 5-12** Radiograph of a patient with a total knee prosthesis inserted 18 months previously (A). The patient had recently experienced increasing pain in the knee; evidence of osteolysis can be seen around the prosthesis, particularly in the tibial component. Such osteolysis can result from either infection or mechanical loosening. An isotope scan (B) shows intense uptake around all of the components of the knee joint, typical of infection. Increased isotope uptake would also occur with prosthetic loosening; however, one would expect it to be limited to the component that had been loosened (usually, in the case of the knee, the tibial component) and to be focal at the sites of maximal movement of the prosthesis.

**Figure 5-13** Radiograph of the ankle of a middle-aged shepherd with a sclerotic lesion of the lower fibula which on biopsy proved to be due to actinomycosis. (Courtesy of Dr. Juan Roig.)
Other complications of chronic osteomyelitis include squamous cell carcinoma, which, in association with a chronic fistula (Marjolin's ulcer), has been reported to be a late sequela of chronic osteomyelitis in about 1% of patients, occurring up to 30 to 40 years after the original infection (Fig. 5-15). Systemic amyloidosis may also be a complication of chronic osteomyelitis.

**Chronic Recurrent Multifocal Osteomyelitis**

Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory condition mimicking osteomyelitis and affecting children and young adults. It is characterized by the insidious onset of low-grade fever, local swelling, and bone pain. Radiologic findings may suggest osteomyelitis, and bone-seeking isotopes reveal other asymptomatic sites of involvement. The lesions occur mainly in the metaphyses of long tubular bones, as well as the clavicles, spine, and pelvis; the lesions are sometimes symmetrically distributed. Cultures are consistently negative. Consequently the suspicion of a round cell malignancy, especially because of periosteal new bone formation in the region of the clavicle, is frequently entertained (Fig. 5-16).

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**FIGURE 5-14** Photomicrograph of tissue obtained from a lesion similar to that shown in Figure 5-13 demonstrates an acute and chronic inflammatory reaction surrounding the typical eosinophilic 'sulfur' granules seen in association with actinomycosis (H&E, × 10 obj.). (Courtesy of Dr. Miguel Calvo.)

**FIGURE 5-15**

A. Cross photograph of the foot and ankle in a patient with long-standing osteomyelitis. Overgrowth of partially ulcerated hyperkeratotic skin is seen in the area of the ankle joint. B. Sagittal section shows a draining sinus from the infected bone opening onto the ulcerated skin. There is invasion of firm white tissue from the skin surface into the underlying soft tissue and bone. C. Photomicrograph of the bone shows that the bone is being invaded by a well-differentiated epidermoid carcinoma (H&E, × 4 obj.).
The clinical course of this obscure disease is characterized by periods of intermittent exacerbations and improvements over a period of several years. Some patients have associated recurrent skin lesions (pustulosis palmo-planteris) that closely parallel the exacerbations of the bone lesions. Acute inflammation, with polymorphonuclear leukocyte predominance, occurs in the early phases of the disease, and fibrosis of the marrow with chronic inflammation occurs in later phases. Microscopically, the most common finding is subacute or chronic inflammation with a predominance of plasma cells. Fragments of necrotic bone with associated multinucleated giant cell are a common finding (Fig. 5-17). Histologic examination does not allow distinction of CRMO from acute or subacute bacterial osteomyelitis. Therefore, microbial workup of the tissue, including polymerase chain reaction (PCR) techniques, is essential in order to establish the diagnosis.

**SAPHO Syndrome**

The acronym SAPHO describes a syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis. The syndrome bears a strong relationship to CRMO, and histologically, the bone lesions in CRMO and SAPHO show similar features. A characteristic feature of SAPHO seen in more than 90% of cases is peripheral arthritis. Treatment is dependent on clinical symptoms.

**Hypertrophic Pulmonary Osteoarthropathy (Marie-Bamberger Syndrome)**

Hypertrophic pulmonary osteoarthropathy involves the formation of symmetric periosteal new bone along the diaphyses of the bones of the appendicular skeleton. This condition is seen in association with both chronic inflammatory conditions and neoplastic diseases of the lung and, less commonly, of other organs. The classic presentation is an adult with complaints of arthralgia or aching bone pain, with or without clubbing of the fingers and toes.

The striking radiographic feature of hypertrophic pulmonary osteoarthropathy is symmetric onion skin periostitis of the shafts of long bones, which is confined to the diaphyses but progresses proximally. Densities in the sites of insertions of ligaments and tendons have also been noted. The patient’s level of serum alkaline phosphatase may be elevated. Although the joints do not show significant radiographic change, patients may have painful effusions that are characteristically non-inflammatory. The arthralgia is usually relieved by aspirin.

On microscopic examination of the affected bone, there is marked periosteal new bone formation. The outer layer of the periosteum may show a mononuclear cell infiltrate. No endosteal bone deposition is seen. Sections of the clubbed finger shows no bone formation but increased and hypervascular soft tissue (Fig. 5-18).
The etiology of pulmonary osteoarthropathy remains obscure. Treatment should be directed at the underlying disease.

Infantile Cortical Hyperostosis (Caffey’s Disease)

Infantile cortical hyperostosis (ICH) is a disease of infants having an autosomal dominant trait with incomplete penetration. The affected infants present with a classic triad of hyperirritability, soft tissue swelling, and palpable hard masses over multiple and often symmetric bones. Patients may be feverish and acutely ill; the disease often follows a recent upper respiratory tract infection.

Laboratory findings in patients with ICH may include an increased erythrocyte sedimentation rate, anemia, and leukocytosis with a shift to the left. These findings have been believed to be highly suggestive of an infection; however, in the vast majority of cases, no organism has been isolated. Recent evidence suggests that a mutation in the alpha-1 collagen type I gene may be causal.

Radiography reveals diffuse, usually symmetric, cortical bony thickening. Many bones are affected but especially the mandible, clavicle, and ribs. Involvement of the long bones occurs less often, and the vertebral column and tubular bones of the hands and feet are usually spared. The radiographic features of ICH evolve in stages. Hyperostoses develop on the outer cortical surface, expand, and then remodel by resorption either at the external surface or at the endocortical surface. In the latter case, there is an expansion of the medullary cavity and the cortex is thin. Epiphyses and metaphyses are typically not involved. Tubular bones may be grossly deformed, with bony bridges sometimes appearing between adjacent bones (forearm, ribs). Microscopically such lesions include not only subperiosteal new lamellar bone formation but also local inflammation. Early on, foci of acute inflammation are confined by the periosteum; they then disrupt the periosteal envelope to blend with contiguous

**FIGURE 5-18** A, Radiograph of the forearm in a patient with carcinoma of the lung shows periosteal bone formation on both the radius and the ulna. In this patient, all of the long bones demonstrated dramatic periosteal new bone. B, Photomicrograph of a biopsy of cortical bone from a patient with pulmonary osteoarthropathy. Note the three layers of new periosteal bone (H&E, × 4 obj.). C, Photomicrograph of a section through an affected terminal phalanx shows marked increased hypervascularity of the soft tissue beneath the nail bed (H&E, × 1 obj.). D, Photomicrograph of the dermis of the nail bed showing increased hyperemia (H&E, × 25 obj.).
tissues (fasciae, muscle, and tendon). In the subacute phase, the periosteum re-establishes itself as an entity with a sheet of fibrous tissue under which new subperiosteal bone is formed. In the late remodeling stage, signs of inflammation disappear, and excess peripheral bone is removed (Fig. 5-19).

ICH usually follows a protracted course with several exacerbations and remissions, but spontaneous recovery usually occurs in a few months.

**Septic Arthritis**

Joint infection may be caused by hematogenous infection of the synovium or decompression of contiguous osteomyelitis (Figs. 5-20 to 5-22), or it may be a consequence of direct inoculation of organisms into a joint following trauma. Septic arthritis is common in neonates and infants, affecting most commonly the hip and less commonly the knee or ankle. The reason the hip is more commonly involved is because of the low attachment of the joint capsule onto the neck of the femur, so that the metaphysis is intracapsular, thus facilitating the spread of infection into the joint. In these patients, severe residual growth disturbances often result from damage to the growth cartilage. For this reason, the importance of early diagnosis and treatment cannot be overemphasized (Fig. 5-23). Another group of patients particularly susceptible to developing septic arthritis are debilitated older adults with rheumatoid arthritis or other chronic inflammatory joint diseases.

The diagnosis is established by joint aspiration, preferably assisted by radiologic image intensification and performed under strict aseptic conditions. The aspirate should be sent immediately to the laboratory for direct smear, aerobic and anaerobic cultures, and antibiotic sensitivity analysis; and to increase the likelihood of bacterial growth, the aspirate should be inoculated into the medium as soon as possible. The phenomenon of an apparently sterile infection may well result from difficulties in recovering and growing the bacteria. (The hip joint, situated deep in the body, is difficult to examine as well as to aspirate, and therefore, the diagnosis of septic arthritis in this joint tends to be delayed, particularly in newborns and infants.)

**FIGURE 5-19**

A. Radiograph of an infant admitted to the hospital with fever and enlargement of the forearm shows extensive periosteal new bone formation causing enlargement of the ulna. In addition, there was thickening and widening of the seventh rib, as well as bilateral thickening of the mandible (not shown here). B. Histologic section of tissue affected by infantile cortical hyperostosis reveals extensive periosteal new bone formation, with vascularized fibrous tissue lying between the bone spicules. Although not seen here, a scattering of chronic inflammatory cells is commonly found (H&E, × 1.25 obj.).

**FIGURE 5-20**

In patients with osteomyelitis, infected fluid material tracks through the bone to the bone surface, initially elevating the periosteum, and finally breaking through the periosteum into the soft tissues to drain onto the skin surface. In instances in which the capsule of the joint is attached below the growth plate (as in the hip), the infection may extend directly into the joint cavity, giving rise to secondary septic arthritis.
Cartilage is particularly susceptible to the action of enzymes released by bacteria and disintegrating inflammatory cells, and consequently, is rapidly destroyed in patients with septic arthritis (Fig. 5-24). For this reason, treatment of the disease should consist of immediate surgical incision and drainage, followed by immobilization of the affected joint. Antibiotic therapy alone is usually insufficient.

**Joint Infection Following Sexually Transmitted Disease**

Suppurative arthritis, which was once a frequent complication of gonorrhea, is now decidedly rare, presumably as a result of early and efficient chemotherapy. However, it is an important diagnostic alternative to bear in mind, because the true nature of the disease is likely to be missed unless a careful history is taken. As with other forms of bacterial arthritis, the knee joints are usually the first to be affected, but multiple joint involvement is much more common in patients with gonorrhea than in those with other types of infection. Unlike other *Neisseria*, *Neisseria gonorrhoeae* do not grow well on simple nutrient agar or at reduced temperature. Furthermore, they do not tolerate drying; thus, care should be taken to inoculate patient samples immediately onto the appropriate agar medium. (In recent years, the identification of certain infectious organisms, including mycobacteria, gonococcus, fungi, and viruses, has been based on the use of luminescent molecules that can be coupled to genetic probes [DNA or RNA] to detect specific hybridization reactions. The advantages of DNA-based tests over culture include more rapid results, equal or better sensitivity, and ease of sample taking.)

Transient inflammatory arthritis may also be a complication of the acute stage of gonorrhea. However, in these cases the arthritis is not caused by bacterial infection of the joint but rather is an immunologic response, often associated with a genetic predisposition. A similar type of arthritis may also complicate cases of nonspecific urethritis and acquired immune deficiency syndrome (AIDS).

Congenital syphilis of the bone is rare. The infantile form involves the metaphyses of multiple bones commonly around the knee (Fig. 5-25). The juvenile form is often in the form of subperiosteal thickening (Fig. 5-26).

In the tertiary stage of adult syphilis, chronic necrotizing and destructive osteomyelitis characterized by heavy infiltration of plasma cells used to be a common occurrence. These lesions, referred to as gumma, were usually seen in the skull and the long tubular bones (Fig. 5-27).
Patients with syphilis may also develop arthritis, either as a result of the extension of gummatous osteitis into a joint or as a complication of congenital syphilis. (Charcot’s joint, a rapidly destructive noninfectious arthritis that frequently complicates tabes dorsalis, is discussed in Chapter 11.)

**Pyogenic Spondylitis**

Pyogenic osteomyelitis of the vertebral column is rare in comparison with infections of the appendicular skeleton, and constitutes less than 1% of all cases of osteomyelitis. The disease can be seen at any age but is most common after the sixth decade. It should always be considered in the differential diagnosis of back pain in the elderly. As already mentioned, the predisposing factors include systemic urinary tract infection, diabetes, and intravenous drug abuse. The lumbar spine is involved twice as frequently as the thoracic spine; the cervical spine is only rarely affected. This variation is probably associated with the source of the primary infection, as well as the route of infection via Batson’s plexus.

Depending on the virulence of the infectious agent, pyogenic spondylitis may manifest as back pain, radiculopathy, or systemic signs of acute infection. Usually, however, the patient presents only with vague localizing symptoms and general malaise. Untreated infection may ultimately result in significant deformity of the spine and severe neurologic deficit.

An abscess in the vertebral body can spread posteriorly to involve the posterior arch and the neural canal resulting in meningitis, or may violate the anterior cortex and ligamentous structures to form paravertebral soft tissue abscesses. Retropharyngeal abscesses may arise from cervical infections, and an abscess in the paraspinal muscle may follow thoracic infections. In the lumbar region, an abscess in the psoas sheath may spread to the groin or even to the popliteal fossa. The adjacent vertebra is often infected by spread along the vertebral ligaments; and in these circumstances, the intervertebral disc becomes sequestrated and may eventually be destroyed (Figs. 5-28 and 5-29).

**RADIOGRAPHIC DIAGNOSIS**

Morphologic changes in individuals with infectious disease cannot be demonstrated on radiographs until the disease is well established, that is, significant bone destruction has occurred, and there is reactive new bone formation. Such difficulties in radiologic diagnosis have been partly solved by other imaging modalities, permitting earlier detection of osteomyelitic foci. For example in the early stages of
osteomyelitis and septic arthritis, changes can usually be observed with magnetic resonance imaging (Fig. 5-30).

In clinical studies, radionuclide uptake has been shown to occur in a sizable percentage of cases 10 to 14 days before changes are evident on radiographs. (Of the many radioactive substances used, technetium polyphosphates appear to produce the best results [Fig. 5-31].) Despite its usefulness, radionuclide imaging has important limitations. First, in some patients multiple ‘hot spots’ are detected in the bones at an early stage of *S. aureus* septicemia, but these ‘spots’ do not necessarily progress to clinical osteomyelitis. (It is not known whether these areas represent false-positive results or aborted bone infection.) Second, experimental and clinical studies have documented rare cases of osteomyelitis that have been confirmed by bacteriologic and histologic studies, even though bone scans were initially negative. (This phenomenon may be explained by impaired blood supply to or infarction of the infected area.) Third, technetium polyphosphate bone scanning performed after fracture or bone surgery does not differentiate bone repair from bone infection.

**FIGURE 5-25** A, A specimen radiograph of the lower end of the femur in an infant born with congenital syphilis. Note the linear area of sclerosis and adjacent lucency in the metaphysis above the region of the growth plate. B, A section through the upper tibia reflects the radiographic findings in A (H&E, × 1 obj.). C, Photomicrograph to show fracture and hemorrhagic granulation tissue in the metaphysis (H&E, × 4 obj.).

**FIGURE 5-26** Photomicrograph showing severe periostitis with fibrosis and chronic inflammation secondary to syphilitic infection (H&E, × 1 obj.).

**FIGURE 5-27** Photograph of a cranium showing thinning and fenestration of the frontal bone, in this case secondary to a syphilitic gumma.
Section II  Response to Injury

Bacterial Diagnosis

The conclusive diagnosis of septic arthritis or osteomyelitis depends on the isolation of the pathogen from the lesion or from blood cultures (Fig. 5-32). Because the blood culture may be positive only in about 50% of patients with acute, untreated hematogenous osteomyelitis, when blood culture has been negative in patients for whom osteomyelitis is a likely diagnosis on the basis of clinical data, direct bone aspiration or surgical biopsy should be carried out. The importance of immediate inoculation into the medium of the material suspected of being infected cannot be overemphasized. Delay in getting the material from the operating room to the microbiology laboratory, and consequently, in plating out and inoculating medium from swabs and tissue obtained from the diseased area, may lead to a reduced number of viable organisms and, therefore, to a false-negative culture.

Morbidity of Osteomyelitis

The presence of bacteria in a bone does not necessarily lead to osteomyelitis. Also, it is generally believed that trauma is an important associated prerequisite, perhaps because it produces venostasis or thrombosis and thus provides a nidus for bacterial growth.

As with most infections, the clinical course of bone infection depends on the interaction between the injurious agent and the host tissue. In other words, the severity of the disease in a patient with osteomyelitis depends on the virulence of the infecting organism, the site of infection, and the patient’s age and general health.

The initial local response to infection with pyogenic bacteria is acute inflammation, resulting in production of a fluid exudate containing polymorphonuclear leukocytes (neutrophils) and fibrin (Figs. 5-33 and 5-34). Continuing exudation raises the local tissue pressure, and because the bone is unable to expand, this pressure cannot be relieved by swelling, as is possible in most tissues. Instead, the only potential space—the vascular space—is compromised, leading to widespread bone death (Fig. 5-35). Indeed, the major clinical problem in treating patients with osteomyelitis is the extent of the osteonecrosis, which interferes with the access of antibiotics.

**Figure 5-28** Photograph of sagittal section through the thoracolumbar spine of a patient with pyogenic spondylitis, showing involvement of several vertebral segments. Mild kyphotic deformity is apparent. Note the complete destruction of the disc by the disease process. (Courtesy of Dr. Krishnan K. Unni.)

**Bacterial Diagnosis**

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**Figure 5-29** A, Radiograph of the lumbar spine of a 55-year-old woman demonstrates the typical appearance of established late-stage septic spondylitis, which in this case was due to *Escherichia coli* secondary to genitourinary infection. There is destruction of the adjacent vertebral end plates of L3 and L4 with some bone sclerosis. A radiograph taken 2 months prior (B) shows no obvious evidence of disease.
FIGURE 5-29—CONT’D  C, Photomicrograph of tissue obtained from the spine showing fragmented bone, granulation tissue, and chronic inflammation (H&E, × 4 obj.). D, Photomicrograph of a portion of the cartilaginous vertebral end plate being destroyed by chronic inflamed granulation tissue (H&E, × 4 obj.). (A&B courtesy of Dr. Alex Norman.)

FIGURE 5-30  Magnetic resonance image showing a well-defined area of increased signal intensity in the medullary space of the midshaft of the femur, representing osteomyelitis in this intravenous drug abuser. There are soft tissue inflammatory changes with multiple small abscesses adjacent to the femur.

FIGURE 5-31  Radiograph of the shoulder in a patient with fever and pain and tenderness at the upper end of the humerus (A). Although some osteolysis may be present, it is difficult to define a lesion. No obvious periosteal reaction has occurred. However, in the isotope scan, intense uptake of radioactive isotope is evident at the upper end of the humerus (B). (A scan frequently demonstrates the presence of osteomyelitis before any changes are evident on radiographs.)
FIGURE 5-32 A. Colonies of *Staphylococcus aureus* are illuminated to show their color and growth characteristics on blood agar. B. Transilluminated to show hemolysis of the blood agar plate around each colony.

FIGURE 5-33 Photomicrograph to illustrate the acute phase of osteomyelitis. The marrow space is filled with acute inflammatory cells but no obvious bone destruction or necrosis is yet evident (H&E, × 10 obj.).

FIGURE 5-34 Photomicrograph of biopsy tissue from a case of osteomyelitis at a slightly later stage than in Figure 5-33 demonstrates a polymorphonuclear leukocyte infiltrate with focal areas of fibrinous exudate. The bone is necrotic and shows focal surface erosion secondary to enzymatic digestion (H&E, × 25 obj.).

FIGURE 5-35 Photomicrograph demonstrates an area of necrotic bone surrounded by an acute inflammatory exudate (pus). A focus of necrotic bone such as this allows the sequestration of bacteria, and unless it is surgically removed, antibiotic therapy may not prevent the development of chronic relapsing osteomyelitis (H&E, × 4 obj.).
In the natural course of events, the exudate is forced through the medullary canal and the haversian systems of the cortical bone to the bone surface. In children, the cortex is thin and the periosteum only loosely attached, so it is easily elevated (Fig. 5-36). New bone from the cambium layer of the periosteum produces a sleeve of reactive bone (the involucrum) around the affected bone segment. In very young children, the involucrum may be massive (Fig. 5-37). In adults (because the periosteum is firmly attached to the cortical bone), the periosteal elevation and new bone formation may be minimal.

In children, the necrotic medullary bone becomes isolated within a large cavity and is referred to as the sequestrum (Fig. 5-38). The sequestrum may consist of a mere wafer of cortex, the devascularized cancellous bone having been absorbed, or it may be a large piece of bone or many small pieces. In adults, a large involucrum and the associated sequestrum formation are much less common. In untreated cases, the pus frequently extends beyond the confines of the periosteum into the soft tissue and ultimately through the skin, forming a draining sinus (Fig. 5-39).

The extent of the bone affected varies from patient to patient. When the entire diaphysis is surrounded by pus, it becomes completely necrotic. If only a small area is devascularized, the affected area may be gradually resorbed and an abscess (Brodie's abscess) will form (Fig. 5-40). The radiographic differential diagnosis of Brodie's abscess might include osteoid osteoma, eosinophilic granuloma, and malignant small cell tumors (Fig. 5-41).

In most patients, bone infection does not result in localized abscesses because necrotic bone undergoes resorption only when there are viable marrow cells to secrete the necessary enzymes and provide active osteoclast phagocytosis.

Osteomyelitis often complicates those diseases that result in vascular insufficiency such as sickle cell anemia, in which patients often experience repeated bone infections (Fig. 5-42). In almost all cases, the infecting organisms are gram-negative rods, most commonly Salmonella (approximately 80%). However, gram-positive bacteria,
particularly *S. aureus*, are also routinely found in these patients. Because the presenting symptoms in individuals with sickle cell disease are often insidious and mimic those of marrow crisis, early blood culture is recommended. Presumptive antibiotic therapy should include agents active against *Salmonella* species. (It should be noted that not all instances of *Salmonella* osteomyelitis are encountered in patients with sickle cell disease [Fig. 5-43].)

Two other bone diseases that may be complicated by ischemia and infection are Gaucher’s disease and osteopetrosis. In patients with Gaucher’s disease, osteomyelitis sometimes follows a biopsy procedure. Therefore, if biopsy is performed on such patients the strictest asepsis is necessary and antibiotic coverage should be considered. In patients with osteopetrosis, the jaw is often affected, probably via tooth infections.

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**FIGURE 5-39** Photomicrograph of a toe removed from a diabetic patient who had developed osteomyelitis. The inflammatory response has led to destruction of the bone and the distal interphalangeal joint (H&E, × 1 obj.).

**FIGURE 5-40** Photomicrograph of a cortical abscess, excised from the femoral neck of a 12-year-old boy, which was mistaken clinically and radiographically for an osteoid osteoma (H&E, × 1 obj.).

**FIGURE 5-41** Radiograph that shows a bone abscess in the upper femoral shaft of a 33-year-old man demonstrating massive bone sclerosis and mature periosteal bone formation. The lack of central calcification in the lytic area together with the age of the patient make a diagnosis of osteoid osteoma less likely. (Courtesy of Dr. Alex Norman.)

**FIGURE 5-42** Radiograph of the arm in a patient with sickle cell disease shows permeative bone destruction of the humerus, with involucrum formation and extensive sequestration. At surgery, these complications were shown to be due to infection.
Granulomatous Inflammation of Bones and Joints

**MYCOBACTERIAL INFECTION (TUBERCULOSIS)**

**Clinical Considerations**

Approximately 1% of patients with granulomatous inflammation (i.e., inflammation characterized by discrete nodules of chronic inflammatory cells and giant cells) develop musculoskeletal complications and the most common site of skeletal involvement is the spine; this is because the most common primary foci of tuberculosis are in the lungs and bowel. Before the advent of modern chemotherapy and before the elimination of bovine tuberculosis in most of the western world, bone and joint tuberculosis was one of the most common indications for admission to an orthopaedic service. In less developed countries, this is still the case. However, in developed countries, tuberculosis has become unusual enough that there is a real risk that it may often remain clinically undetected and the true nature of the disease becomes apparent only after the pathologist has examined the tissue.

There is increased risk for mycobacterial infection in individuals with chronic debilitating conditions including narcotic addicts, therapeutically immunosuppressed patients, and those with AIDS. In patients with AIDS, miliary mycobacterial disease may present as an acute febrile illness. However, in most patients, the onset of symptoms is likely to be insidious and includes local pain as well as systemic signs of chronic debilitating illness.

Osseous disease is caused by metastatic spread of the mycobacterium from elsewhere in the body, usually from the lungs; in most patients, bony foci of infection coexist with arthritis, and multiple skeletal lesions are not uncommon. Skeletal manifestation of infection most often occurs in the spine (Figs. 5-44 and 5-45); the next most commonly affected area is the hip (Figs. 5-46 and 5-47), followed by the knee (Fig. 5-48). However, any joint may be involved, including those of the hand.

In general, osseous disease is most common in patients younger than the age of 25 years and both sexes are equally affected. The spine and hip are more commonly affected in children, and the knee is more common in adults.

In 1779, Percival Pott described the clinical presentation of paraplegia associated with the characteristic gibbus formation that bears his name, and the lower thoracic spine is the most frequent site of tuberculous spondylitis, with involvement of several vertebral bodies in more than 50% of cases. The disease often begins in one vertebral body and spreads underneath the spinal ligaments to affect other vertebrae. In untreated patients, this course of events eventually leads to vertebral collapse and angulation of the vertebral column (Fig. 5-49).

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**FIGURE 5-43** Radiograph of a middle-aged woman who was in good general health except for pain in the right ankle. The x-ray study was interpreted as being most consistent with a giant cell tumor. Biopsy proved the lesion to be inflammatory, and *Salmonella typhosa* was isolated by culture.

**FIGURE 5-44** Anteroposterior radiograph of the spine (A) shows narrowing and destruction of the intervertebral disc at the level of T11–T12. Note also the paravertebral soft tissue swelling. In the lateral radiograph (B), destructive bone disease is seen anteriorly in the 11th and 12th thoracic vertebrae. This lesion was proved to be due to tuberculosis.
At the time of presentation, the patient with tuberculous spondylitis may have radiculopathy caused by compression of the spinal cord or nerve roots. The disease may also spread to the meninges, with subsequent tuberculous meningitis.

As described by Pott, paraplegia was the most serious complication before the advent of antibiotic therapy. Paraplegia is caused by extension of the disease process into the peridural space with resultant pressure on the cord. (This may be accentuated by the mechanical pressure associated with bone deformity and dislocation of affected segments may lead to sudden paraplegia.)

Because the initial lesion is most often seen in the lower thoracic spine, the psoas muscle sheath is frequently involved in the process. Patients may present with a fluctuant swelling, or cold abscess, in the groin or elsewhere as the result of tracking of the infected material from the paraspinal area.

**Radiographic Findings**

Radiographic examination of an involved joint shows osteopenia and soft tissue swelling early in the disease. These changes are followed by marginal erosion of the bone and destruction of the subchondral bone, with narrowing of the joint space.
In non-weight-bearing joints such as the shoulder, but also occasionally in the knee joint, subchondral lysis may occur without obvious joint destruction and narrowing. In such cases, which are sometimes referred to as caries sicca, the lesion may mimic a tumor radiographically, and so, in the shoulder, may be mistaken for a chondroblastoma (Fig. 5-50).

In the spine, radiographic examination may show focal bony destruction with disc involvement and vertebral collapse. Unlike pyogenic osteomyelitis, reactive new bone and hypertrophied osteophyte around the infected focus are not common.

The primary granulomatous abscess may be located in the vertebral body either anteriorly, paradiscally, or centrally, giving rise to three characteristic radiographic presentations (Fig. 5-51).

The anterior lesion, which accounts for approximately 20% of cases, usually leads to cortical bone destruction under the anterior longitudinal ligament. As the ligament lifts off the vertebral margin, infection spreads to the adjacent vertebral segment.

The paradiscal lesion, which accounts for over half of the cases, begins in the vertebral metaphysis and erodes through the cartilaginous end plate, extending around and sequestrating the disc to extend into the adjacent vertebra. Disc space narrowing, bone destruction with subsequent kyphotic deformity, and eventual intervertebral body fusion occur, usually after 1 to 2 years.

The central lesion, which accounts for the remaining cases, begins in the mid-portion of the vertebral body. It then spreads to involve the entire vertebral body, leading to vertebral collapse and usually to pronounced gibbus deformity (Fig. 5-52).

Pathologic Findings

Gross examination of the areas affected by tuberculosis is likely to show thickened edematous tissue, frequently studded with small grayish nodules, sometimes with white opaque centers (granulomas). These granulomas often become confluent and produce larger areas of white necrotic material, often called caseation (or cheesy) necrosis. In a joint separation of the articular cartilage, dissected from the underlying bone by granulomatous tissue, is a characteristic feature. In the later stages of untreated disease, ankylosis is a frequent complication.

On microscopic examination, the typical granuloma (Figs. 5-53 and 5-54) consists of a central necrotic area surrounded by pale histiocytes, sometimes referred to as epithelioid cells. Among the epithelioid cells are some scattered giant cells, the nuclei of which are...
Section II  Response to Injury

Typically arranged at the margin of the cell (Langerhans’ giant cells). At the periphery of the tubercle is a rim of mixed chronic inflammatory cells. Often the granulomas are confluent, resulting in extensive central caseation necrosis. The acid-fast bacilli (AFB) can be demonstrated with the Ziehl-Neelsen stain, and are characteristically seen in the giant cells and at the margin of the caseous area.

Atypical Mycobacterial Disease

Patients who are severely immunocompromised, in particular those with advanced human immunodeficiency virus (HIV) infection, are at risk for disseminated mycobacterial disease, usually Mycobacterium avium complex (Fig. 5-55). Bone infection in these patients, as in others with severe immunodeficiency diseases, can be difficult to detect because local redness and swelling may be absent and the patient afebrile. Typical granulomas are often absent and microscopically, only large numbers of histiocytes with admixed acute and chronic inflammatory cells may be present. However, acid-fast staining reveals large numbers of intracellular mycobacteria—many more than are seen in a patient with the typical presentation of tuberculosis (Fig. 5-56). In general, diagnosis depends on imaging techniques in conjunction with careful clinical assessment.

In addition to M. avium-intracellulare, nontuberculous mycobacteria causing osteoarticular infections include Mycobacterium fortuitum group, Mycobacterium marinum, Mycobacterium kansasii, Mycobacterium abscessus, and Mycobacterium chelonae. All nontuberculous mycobacteria are ubiquitous in the environment (soil, water, animals, and birds), and although they are generally less pathogenic than Mycobacterium tuberculosis, they do cause a variety of infections. Notably, though, as with most...
infecting microbes, the intrinsic virulence of mycobacterial species is not the sole factor determining clinical outcome. The genetic background as well as the immune status of the infected individual play an important role in the expression of mycobacterial disease.

Nontuberculosis mycobacteria can cause a variety of chronic granulomatous infections affecting tendon sheaths, bursae, bones, and joints after direct inoculation through accidental trauma, surgical incision, puncture wounds, or injections. Not surprisingly then, there have been a number of recent reports of acupuncture mycobacteriosis due to *M. chelonae*, an organism commonly colonizing instruments or growing in contaminated water and difficult to kill with regular cleaning and disinfection methods. An association may not be made between the inoculating procedure (i.e., acupuncture) and the clinical illness because the infection has such a long incubation period.
Osteomyelitis may also follow infection with *M. marinum*, a common aquatic organism. The bacteria are inoculated into traumatized skin, often by a fish hook, exposed to contaminated water (or fish). Clinical disease typically begins with small papules that become suppurative. Infection, which can take up to 4 weeks to develop, is usually localized to distal portions of the upper extremities and may resolve spontaneously (Fig. 5-57). However, dissemination to bursa, joints, and bone has been reported in both immunocompetent and immunocompromised people. *M. marinum* infection can easily be misdiagnosed as gout, rheumatoid arthritis, tendinitis, or sterile abscesses. Antibiotic therapy can prove difficult because the organism is resistant to many conventional antimicrobial agents.

Management of nontuberculosis mycobacterial bone and joint infections always require surgical débridement. Drug therapy for specific pathogens is also essential. Identification of the organisms increasingly focuses on rapid diagnostic systems (including high-performance liquid chromatography, PCR, and genetic probes).

**SARCOIDOSIS**

About 10% of patients with sarcoidosis have an episode of joint involvement. In most cases, this is a migratory acute polyarticular disease, often symmetric and of only a few weeks’ duration. Hilar lymphadenopathy and erythema nodosum are frequently associated. In a small number of patients, a chronic granulomatous arthritis may present in a large joint and is generally monoarticular. The lesion is most likely to be mistaken for tuberculosis (Fig. 5-58). However, certain histologic features help to distinguish sarcoidosis from tuberculosis: the formation of well-delineated tight granulomas; the lack of caseation necrosis; the increased prominence of large, pale epithelioid cells with fewer chronic inflammatory cells; and the absence of AFB. (With regard to the last point, it should be noted that it is frequently difficult to demonstrate AFB in patients with bone and joint tuberculosis. In any individual suspected of having granulomatous tissue, smears should be taken for direct examination, and cultures for tuberculosis, brucellosis, fungus, and atypical mycobacteria should be prepared. In general, a firm diagnosis can be made only when positive cultures have been obtained.)

About 5% of patients with early acute or subacute sarcoidosis are found to have asymptomatic bone changes on routine radiography of the hands, feet, and occasionally in other bones (Figs. 5-59 and 5-60). The most common clinical finding in sarcoid dactylitis is soft tissue swelling over the affected digits, with tenderness and stiffness of the adjacent joints; the overlying skin may be erythematous. When the terminal phalanges are involved, the nails may show thickening and ridging. In severe cases, the affected bones may be completely resorbed, leading to virtual disappearance of the phalanges, sometimes complicated by pathologic fractures and marked deformity. Rare cases of sarcoid present primarily as multiple bone lesions (Figs. 5-61 and 5-62).
As with tuberculosis infections, fungal infections are likely to be seen more frequently in debilitated patients, especially immunocompromised individuals. The spine, as well as other bones and joints, can be affected by mycotic infections, with the lung being the usual portal of entry. The radiographic and pathologic features are similar to those of tuberculosis. For this reason, when granulomatous infection is found or suspected, it is important to make direct smears and to prepare cultures not only for acid-fast organisms but also for fungi. Common fungal conditions that have been found to be responsible for granulomatous infections include blastomycosis, coccidioidomycosis, cryptococcosis, candidiasis, and sporotrichosis.

**Blastomycosis**

Blastomycosis is endemic in the southeastern and south central states of the United States, as well as Canadian provinces that border the Great Lakes. *Blastomyces dermatitidis* is the asexual stage of *Ajellomyces dermatitidis*. *Blastomyces dermatitidis* is dimorphic—growing as a mycelial form at room temperature and transforming into a yeast form at 37 °C. Initial infection is through the lungs and generally subclinical. The organism may be carried throughout the body via blood, culminating in disease with protean manifestations. The most common skeletal sites are the vertebrae, ribs, tibia, and the tarsal and carpal bones. Vertebral disease is easily confused with tuberculosis, with anterior involvement of the vertebral body, interspace destruction, and development of large paraspinal abscesses. Therefore, if the vertebrae are involved, radiographic differentiation from tuberculous spondylitis can be difficult (Fig. 5-63). Microscopic examination of a stained smear of sputum, pleural fluid, or pus from the affected part will reveal the characteristic thick-walled, budding yeast cells.

**Coccidioidomycosis**

Coccidioidomycosis, also known as San Joaquin Valley fever, is caused by the fungus *Coccidioides immitis*. There is a high incidence of this disease in the arid southwestern United States. The
bone lesions are usually lytic, with indiscriminate involvement and destruction of vertebral bodies, neural arches, and even contiguous ribs. Late changes of vertebral collapse may render differentiation from tuberculous spondylitis difficult (Figs. 5-64 and 5-65).

Cryptococcosis
Skeletal cryptococcosis often occurs secondary to cases of chronic meningoencephalitis caused by Cryptococcus neoformans. The pelvis, femur, spine, and tibia are among the most common sites of involvement. Patients usually present with pain, swelling, and tenderness over the affected part. Radiographically, these lesions present as radiolucencies with or without local subperiosteal new bone formation. Histologically, the lesions reveal granulation tissue containing multinuclear giant cells, lymphocytes, and histiocytes. The presence of the yeast-like cryptococci may be demonstrated by periodic acid–Schiff (PAS) and Gomori methenamine-silver (GMS) stains.

Other Fungal Infections
Sporotrichosis infection may result from the direct contamination of a joint by a puncture wound from the thorn of a contaminated plant (often a rose).

Very rarely, other molds found in soil may result in infection. In Figure 5-66, a patient with a 1-year history of a discrete swelling in the finger was diagnosed clinically and radiographically as a neoplasm, which was possibly malignant. The lesion turned out to be inflammatory, and the rare organism Exophiala jeansi was cultured.

Immunocompromised patients with long-term indwelling intravenous catheters (e.g., for parenteral nutrition) occasionally develop bone and joint infections due to Candida or Aspergillus.

Because blood cultures are most likely to be negative, biopsy may be necessary for diagnosis of fungal infections.

Parasitic Infections
Echinococcal Cysts
Echinococcal cyst (hydatid cysts) are commonly seen in the bones of patients from sheep-raising countries in which the disease is endemic (Spain, Greece, and the Middle East). The cyst is often seen initially at the epiphyseal end of the bone, usually affecting the spongiosa because localization is dependent on hematogenous dissemination. It should be noted that hydatid echinococcosis developing
FIGURE 5-61 A 31-year-old man presented with history of headache. A and B, Computed tomography scan of the skull shown here revealed numerous lytic defects in the calvarium. C, A biopsy of one of the lesions in the skull revealed histiocytic and giant cell granuloma (H&E, × 25 obj.).

FIGURE 5-62 A, Anteroposterior radiograph of a 55-year-old female with multiple sclerotic lesions of the pelvis. B, Computed tomography scan of the same patient. Biopsy proved the lesions to be sarcoidosis.

intraosseously does not resemble the classic unilocular hydatid of soft tissue. Rather, it is usually a multiloculated lesion, with an irregular outline that can be easily confused with a tumor on radiographs. This is because the resistance offered by the osseous tissue causes the larva to develop by exogenous budding, resulting in the presence of many small cysts growing outside the original focus of implantation. Scolices rarely develop in these cysts, and therefore, they are usually sterile. Only when the cyst erupts to the surrounding soft tissue does the lesion assume the more conventional large unilocular appearance (Figs. 5-67 and 5-68).
FIGURE 5-63 Anteroposterior (A) and lateral (B) radiographs of the thoracic spine demonstrate multiple destructive lesions involving several vertebral bodies, some of which are partially collapsed. Biopsy proved this to be due to blastomycosis.

FIGURE 5-64 Radiograph of the knee of a 60-year-old man complaining of mild pain for a few months. The film shows a poorly defined lytic lesion extending from the articular surface of the tibia into the diaphysis. The cortex appears intact. Biopsy proved this to be the result of infection with coccidioidomycosis. (Courtesy of Dr. A. Roessner.)

FIGURE 5-65 A, Low-power photomicrograph of tissue obtained from a patient with chronic spinal disease resulting from infection with Coccidioides immitis. The marrow space is infiltrated by chronic inflammatory tissue (H&E, × 4 obj.). B, High-power view of the same tissue reveals two rounded, thick-walled fungal organisms containing endospores (H&E, × 100 obj.).
FIGURE 5-66 A. Magnetic resonance imaging (MRI) scan of a well-demarcated lesion on the volar surface of the middle finger present for 1 year in a 38-year-old woman. B, Sectional MRI scan shows well-defined lesion with a heterogeneous signal. C, Photomicrograph of the resected tissue reveals acutely inflamed histiocytic tissue (H&E, ×10 obj.). D, Photomicrograph of tissue stained with periodic acid–Schiff stain reveals septate hyphae (×50 obj.). E, Cultured colony of Exophiala jeanselmei.
FIGURE 5-67  A, Gross photograph of the upper end of a femur removed at necropsy from a patient with hydatid disease. The medullary cavity is filled with glistening white nodular tissue, which on closer examination, was made up of fibrous walled cysts. B, Radiograph of the same specimen shows a multiloculated lytic appearance and irregular thinning of the cortices. In those parts of the world where the occurrence of hydatid disease is rare, such radiographic findings will probably be interpreted by the radiologist as a tumor. C, Gross photograph of the many small cysts that are characteristic of echinococcal infestation of the bone. D, Photomicrograph of material removed from a hydatid cyst reveals a scolex with hooklets (H&E, × 100 obj.).
FIGURE 5-68  A 60-year-old man suffered a comminuted fracture following a fall. At the time of this x-ray study, no comment was made regarding a pathologic fracture. The fracture was treated by intramedullary rodding. Three and a half years later, the patient presented with the radiographs shown here (B). At operation, massive necrotic debris and granulation tissue together with membranous and cystic material as shown here were excised (C). The histology reveals irregular remnants of chitinous laminated hyaline material consistent with echinococcal cyst (D) (H&E, × 4 obj.). History revealed that 20 years before the fracture, he had worked as a farm laborer with sheep and dogs.
Metabolic Disturbances

CHAPTER 6

Diseases Resulting from Synthesis of Abnormal Matrix Components

<table>
<thead>
<tr>
<th>Disturbances in Collagen Synthesis, 142</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteogenesis Imperfecta, 142</td>
</tr>
<tr>
<td>Ehlers-Danlos Syndrome, 149</td>
</tr>
<tr>
<td>Marfan’s Syndrome, 151</td>
</tr>
<tr>
<td>Mucopolysaccharidoses, 152</td>
</tr>
</tbody>
</table>

| Morquio’s Syndrome, 152                 |
| Hurler’s Syndrome, 155                  |

<table>
<thead>
<tr>
<th>Disturbances in Mineral Formation, 156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatasia (Phosphoethanolaminuria), 156</td>
</tr>
<tr>
<td>Fluorosis, 157</td>
</tr>
<tr>
<td>Dwarfism (Chondro-osseous Dysplasia), 158</td>
</tr>
</tbody>
</table>
Body mass is mostly accounted for by the connective tissues and skeletal muscle, and although the final adult size of an individual (height, weight, build) is the result of many complex factors, both genetic and extrinsic (e.g., diet and activity level), perhaps the most important determinant is the total number of connective tissue cells involved in production of the extracellular matrix and the quantity of extracellular matrix produced by each cell. Especially important to skeletal size is the optimal functioning of the epiphyseal growth plate during the period of development.

The mechanical strength of the connective tissues depends on the synthesis by osteoblasts, chondroblasts, and fibroblasts of organic extracellular matrix constituents (including collagen, proteoglycan [PG], and other noncollagenous proteins), both of the right type and in the right amount. Disease resulting from abnormal synthesis of matrix will interfere with both size and mechanical function.

Disturbances in collagen synthesis may be congenital, as in osteogenesis imperfecta (OI), or acquired, as in scurvy. The disturbance may be intracellular, as in both OI and scurvy, or extracellular, as in some cases of Ehlers-Danlos syndrome (EDS) (Fig. 6-1). However, whether congenital or acquired, pretranslational or post-translational, all of these conditions give rise to abnormalities in the connective tissue matrices that affect the mechanical properties of the skeleton.

The mechanical properties of the bony skeleton depend not only on the organic matrix, but also on the calcification of the organic matrix. This, in turn, depends not only on adequate amounts of calcium and inorganic phosphates in the tissue fluid but also on the exercise of cellular control by means of the positive and negative influences of many substances, including alkaline phosphatase.

In this chapter, the most important of the diseases resulting from disturbances in both organic and inorganic matrix synthesis will be discussed.

![Schematic representation of sites of possible disturbance in collagen synthesis leading to various disorders.](image)

### Disturbances in Collagen Synthesis

#### OSTEGENESIS IMPERFECTA

**Clinical Evaluation**

OI (brittle bone disease) is the most commonly recognized congenital disease affecting the production of collagen. It involves the bone matrix as well as other connective tissues. The disease comprises a number of distinct syndromes having in common propensity to fracture and clinical evidence of osteopenia. Most of these syndromes are inherited as an autosomal dominant trait, rarely as a recessive trait, and still others occur as spontaneous mutations. Many patients have poorly formed dentin, hearing loss, and EDS–like features; however, it is the susceptibility to fracture that gives rise to most of their clinical problems. On the basis of clinical as well as genetic features, eight distinct groups have been described.

**TYPE I**

- Most common and mildest type of OI (including least number of fractures).
- Most fractures occur before puberty.
- Normal or near-normal stature.
- Loose joints and muscle weakness.
- Sclera usually have a blue or gray tint.
- Triangular face.
- Bone deformity absent or minimal.
- Brittle teeth possible.
- Hearing loss possible, often beginning in early 20s or 30s.
- Collagen structure is normal, but the amount is less than normal.

**TYPE II**

- Most severe form.
- Frequently lethal at or shortly after birth, often due to respiratory problems.
- Numerous fractures and severe bone deformity.
- Small stature with underdeveloped lungs.
- Sclera have blue-gray tint.
- Collagen improperly formed.

**TYPE III**

- Bones fracture easily. Fracture often present at birth, and x-ray studies may reveal healed fractures that occurred before birth.
- Short stature.
- Sclera have a blue-gray tint.
- Loose joints and poor muscle development in arms and legs.
- Barrel-shaped rib cage.
- Spinal curvature.
- Respiratory problems possible.
- Bone deformity, often severe.
- Brittle teeth possible.
- Hearing loss possible.
- Collagen improperly formed.

**TYPE IV**

- Between type I and type III in severity.
- Bones fracture easily, most before puberty.
- Shorter than average stature.
- Sclera are normal in color.
- Mild to moderate bone deformity.
- Tendency toward spinal curvature.
- Barrel-shaped rib cage.
Triangular face.
Brittle teeth possible.
Hearing loss possible.
Collagen improperly formed.

**TYPE V**
- Clinically similar to type IV in appearance and symptoms of OI.
- A dense band seen on x-ray studies adjacent to the growth plate of the long bones.
- Unusually large calluses, called hypertrophic calluses, at the sites of fractures or surgical procedures.
- Calcification of the membrane between the radius and ulna restricting forearm rotation.
- White sclera.
- Normal teeth.
- Bone has a “mesh-like” appearance when viewed under the microscope and a distinguishing feature are patches of bone that have failed to mineralize.

**TYPE VI**
- Clinically similar to type IV OI in appearance and symptoms.
- The alkaline phosphatase activity level is slightly elevated.
- Bone has a distinctive “fish-scale” appearance microscopically.
- Diagnosed by bone biopsy.
- Whether this form is inherited in a dominant or recessive manner is unknown.
- Very few people with this type of OI have been identified.

Two forms of OI that are inherited in a recessive manner were discovered in 2006. Both types are caused by genes that affect collagen formation.

**TYPE VII**
- Resembles type IV OI in many aspects of appearance and symptoms.
- In other instances, the appearance and symptoms are similar to type II lethal OI, except infants have white sclera, a small head, and a round face.
- Short stature.
- Short humerus and short femur.
- Coxa vara is common; the acutely angled femur head affects the hip socket.
- Results from recessive inheritance of a mutation to the cartilage-associated protein (CRTAP) gene.

**TYPE VIII**
- Resembles lethal type II or III OI in appearance and symptoms except that infants have white sclera.
- Severe growth deficiency.
- Extreme skeletal undermineralization.
- Caused by a deficiency of prolyl 3-hydroxylase 1 (P3H1) due to a mutation to the LEPRE1 gene.

These various syndromes have many clinical features in common. The majority of patients are short in stature, and the most severely affected cases are dwarfed. However, the incidence of fracture varies considerably depending on the type of the disease and age; fractures are more common in children than in adults (Fig. 6-2). The standard treatment of fractures by immobilization results in disuse osteoporosis, which in patients with OI further increases the tendency to fracture, thereby setting up a vicious circle (Fig. 6-3). Thus, once a fracture has occurred, these unfortunate individuals have a tendency toward repeated fractures in the same area.

The presence in many patients of blue sclerae (Fig. 6-4), poorly formed dentin (Fig. 6-5), and ligamentous laxity confirm that the disease is not confined to the skeleton but is rather a generalized disorder of the connective tissues. Collagen synthesis by the osteoblasts and other connective tissue cells is deficient quantitatively (Table 6-1) and has been shown to differ qualitatively in many patients. Based on linkage analysis, it has been concluded that 90% of typical familial cases of OI are linked to abnormalities in collagen type I genes. Mutations in OI affect the type I collagen loci COL1A1 and COL1A2. The commonest are nucleotide substitutions or less commonly splicings or small deletions.
The radiologic appearances in a case of OI depends on the severity of the clinical disease, but the hallmark of the disease is osteopenia, associated with evidence of multiple fractures and, in severe disease, deformities (Fig. 6-6). The entire skeleton is affected, but the lower limb more obviously so.

In the spine, platyspondyly and biconcavity are evidence of compression fractures in the vertebral bodies, and in many cases, these multiple fractures contribute to kyphoscoliosis (Fig. 6-7). Odontoid fractures are a rare complication, occurring mostly in children. In the severely affected patient, the pelvis is often markedly deformed and sometimes referred to as being triradiate in appearance.

The skull films reveal a large vault with temporal bulging and typically a small triangular face beneath. Multiple centers of ossification may be observed in the skull, particularly in the occipital portion (wormian bones) (Fig. 6-8). Occasionally, there is a ‘hair on end’ appearance. Basilar impression with deformity and encroachment upon the foramen magnum may lead to compression of the medulla oblongata.

In the lethal type II OI, the long bones are wide in diameter with thin shell-like cortices and multiple fractures, giving rise to telescoping of the bones (Fig. 6-9). In most other cases of severe clinical OI, however, the long bones are very slender (Fig. 6-10). The ribs may be so attenuated that one sees a ribbon-like configuration suggestive of neurofibromatosis.

Fractures vary in number, depending on the severity of the disease, but they are commonest in the lower limbs. Usually they heal at the normal rate. The number of fractures sustained each year is maximal in the growing period and decreases after adolescence. Fractures again become a problem with aging and the onset of senile osteoporosis. Hypertrophic callus develops in a few cases notably (type V) resulting in excessive swelling, heat, throbbing pain, and tenderness. It is important to distinguish this condition of hypertrophic callus from acute osteomyelitis and osteosarcoma (Fig. 6-11).

Many patients, particularly those with the severe form of the disease, are treated surgically with intramedullary rods, which both correct deformity and help to prevent further fracture. Complications associated with this procedure include breakage of the rod, cutting out of the bone at one end of the rod associated with the continuing growth of the bone, and migration of the rod. Infection around the rods is very rare.

The radiographic differential diagnosis of OI in the newborn might include congenital hypophosphatasia (vitamin D–resistant rickets), although in that condition, the alkaline phosphatase level is abnormally low. In a young child, the differential diagnosis might include battered baby syndrome or the early stages of leukemia. In the preadolescent, the condition of juvenile osteoporosis might have to be considered.

![FIGURE 6-4 Osteogenesis imperfecta: clinical photograph showing blue sclerae. The color results in part from the thinness of the sclerae.](image)

**Radiographic Features**

The radiologic appearances in a case of OI depends on the severity of the clinical disease, but the hallmark of the disease is osteopenia, associated with evidence of multiple fractures and, in severe disease, deformities (Fig. 6-6). The entire skeleton is affected, but the lower limb more obviously so.

In the spine, platyspondyly and biconcavity are evidence of compression fractures in the vertebral bodies, and in many cases, these multiple fractures contribute to kyphoscoliosis (Fig. 6-7). Odontoid fractures are a rare complication, occurring mostly in children. In the severely affected patient, the pelvis is often markedly deformed and sometimes referred to as being triradiate in appearance.

![FIGURE 6-5 Two examples of the appearance of teeth in patients with osteogenesis imperfecta. A. Brown short teeth result from failure in the formation of dentin (dentinogenesis imperfecta). B. When seen from above, the enamel appears to be normal.](image)

| TABLE 6-1 Summary of Histologic Findings in Osteogenesis Imperfecta |
|---------------------------------|-----------------|-----------------|----------------|----------------|
| Osteocytes/Fractional Area of Bone | Fields of Woven Bone |
|---------------------------------|-----------------|----------------|----------------|
| **Control (age matched)** | 242 | 60 | 153-359 | P < 0.001 | – | – | – |
| **Osteogenesis imperfecta (all cases)** | 614 | 214 | 284-1443 | P < 0.001 | 7.68 | 4.30 | 3-17 |
| **Osteogenesis imperfecta (more severe)** | 725 | 345 | 340-1443 | P < 0.001 | 11.28 | 3.35 | 7-17 |
| **Osteogenesis imperfecta (less severe)** | 563 | 127 | 468-773 | P < 0.001 | 5.12 | 2.53 | 3-10 |

Chapter 6

Diseases resulting from synthesis of abnormal matrix components

Figure 6-6 Radiograph of upper extremity in a patient with severe osteogenesis imperfecta shows osteoporosis, slender bones, and multiple healed fractures.

Figure 6-7 Dissected specimen of spine (A) shows scoliosis subsequent to multiple compression fractures. Specimen radiograph of spine (B) demonstrates the underlying osteoporosis.

Figure 6-8 A, Skull from a 9-year-old child shows an open posterior fontanelle and multiple wormian bones. B, Specimen radiograph to show wormian bones.

Figure 6-9 Specimen radiograph of lower limb from a stillborn with type II (lethal) osteogenesis imperfecta showing wide telescopic bones.

Figure 6-10 Radiograph of the leg of a patient with severe clinical osteogenesis imperfecta, which has been treated by rodding of the tibia. The extreme attenuation and ribbon-like quality of the bones is obvious in the fibula.
Approximately 50% of the growing (epiphyseal) ends of the bones in children with moderate to severe OI whose roentgenograms the author has reviewed have a collection of rounded, scalloped radiolucenties with sclerotic margins. In some cases, this is accompanied by a ballooned-out epiphysis and metaphysis, giving a 'bag of popcorn' appearance similar to that described by Fairbank as cystic (Fig. 6-12). These lesions are seen in the long bones, most commonly in those of the lower limb with equal incidence on the right and left sides of the body. In all instances where such lesions occur, the cartilaginous growth plate is irregular and either partially or completely absent (Fig. 6-13).

FIGURE 6-11 A, Radiograph of the femur of an adolescent patient with osteogenesis imperfecta (type V), who developed a rapidly growing, hot tumor following injury. Radiographically, a neoplasm was suspected. B, Photomicrograph of a biopsy obtained from the mass demonstrates cellular immature bone and cartilage consistent with fracture callus (H&E, × 10 obj.).

FIGURE 6-12 Radiograph of knee joint in an 8-year-old child with severe osteogenesis imperfecta. The epiphysis and metaphysis of the femur contain nodular popcorn lesions with radiolucent centers and radiodense margins. No growth plate is seen in the femur. In the tibia, the growth plate is partially visualized (arrow), but the central portion is disrupted.

FIGURE 6-13 Lateral radiograph of the knee in a patient with severe osteogenesis imperfecta. There is irregularity and disruption of both the femoral and tibial growth plates, although less severe than that shown in Figure 6-12.
In the cases with 'popcorn' epiphyses, films obtained during the neonatal period show normal epiphyses and growth plates, indicating that the lesions are not congenital. Films taken after the adult state has been achieved were available for review in 40% of the patients, and in all of these cases, the epiphyseal changes had resolved. A summary of the radiographic findings is shown in Table 6-2.

**Pathologic Features**

Gross examination of the bones reveals a generalized loss of bone tissue, with thin, eggshell-like cortices and very little medullary cancellous bone. Many specimens demonstrate recent or healed fractures, with angulation or bowing, or both (Fig. 6-14).

In general, the epiphyseal ends of the long bones, including the articular surfaces, retain a recognizable shape, although in proportion to the rest of the bone, they appear larger and may show irregularity of the articular surface (Fig. 6-15). The secondary centers of ossification are often markedly distorted and may contain small cartilaginous nodules 1 to 4 mm in diameter (Fig. 6-16).

The appearance of the growth plate varies widely, ranging from normal, to exhibiting one or more indentations secondary to fracture, to total disruption of its regular outline. These latter changes correspond to the scalloped or popcorn lesions seen on radiographic examination and are most probably secondary to trauma. The fragmentation of the growth plate might be reasonably expected to interfere with normal growth.

On microscopic examination, the growth plate fragments show polarized maturation and columnization of the chondrocytes with peripheral ossification. Microscopic examination of an intact growth plate from an OI patient may also reveal some disorganization of the proliferative and hypertrophic zones, with increased permeation of the cartilage by metaphyseal blood vessels and decreased thickness of the calcified zone of the growth plate cartilage. The primary spongiosa on the metaphyseal side is usually extremely scanty and of immature woven bone (Fig. 6-17).

**TABLE 6-2** Summary of Radiographic Findings in Osteogenesis Imperfecta

<table>
<thead>
<tr>
<th></th>
<th>Clinically Less Severely Affected Osteogenesis Imperfecta</th>
<th>Clinically More Severely Affected Osteogenesis Imperfecta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texture</td>
<td>Osteopenia</td>
<td>Proportional to the severity of the clinical disease</td>
</tr>
<tr>
<td>Fractures</td>
<td>Frequency 1–4 per year; generally seen during growth period; most frequent in lower limbs; fractures may be present at birth, but not commonly; deformities usually confined to lower limbs, most often the tibia and fibula</td>
<td>Fractures present at birth; many fractures each year; occur in all four limbs, but always associated with severe deformities</td>
</tr>
<tr>
<td>Long bones</td>
<td>Usually slender</td>
<td>May be widened during infancy to telescoping; in older patients, usually very slender</td>
</tr>
<tr>
<td>Epiphyses</td>
<td>Usually normal in appearance, although irregularities may be present around the knee</td>
<td>Frequently irregular with failure to recognize a normal growth plate, and replacement by bubbly calcified nodules; most frequently seen in lower femur, upper tibia, upper femur, and upper humerus</td>
</tr>
<tr>
<td>Spine</td>
<td>Osteopenia; platyspondyly; mild sclerosis</td>
<td>Severe osteopenia with biconcave vertebrae and frequently severe kyphoscoliosis</td>
</tr>
<tr>
<td>Ribs</td>
<td>Normal</td>
<td>Frequent deformities with thinning, malunited fractures</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Normal</td>
<td>Triradiate</td>
</tr>
</tbody>
</table>

**FIGURE 6-14** Dissected specimen of forearm bones shows multiple fractures, including fracture dislocation of the radial head.

**FIGURE 6-15** Upper end of tibia shows relative enlargement of the cartilaginous end of the bone and marked narrowing of the shaft of the fibula.
Biopsy specimens from patients with the severe form of the disease are characterized by large areas of osseous tissue devoid of an organized trabecular pattern. Examination of the individual trabeculae reveals plump osteoblasts crowded along prominent osteoid seams, and large oval osteocytes surrounded by a small amount of matrix, which more often than not has a woven pattern (Fig. 6-18).

Even in areas that display a lamellar pattern, the lamellae are thin. The osteoclasts appear to be morphologically normal, although both they and the resorptive surfaces are more numerous.

Bone specimens from clinically less severely affected patients are characterized by a predominantly fine lamellar pattern, with areas of woven bone associated with fractures. Although osteoblasts are increased in number, they appear smaller, more spherical, and less numerous than their counterparts in the severe group. Osteoid seams are prominent, probably due to an increased rate of bone formation. The osteocytes, although more mature in appearance than in severely affected patients, are more numerous, larger, and less homogeneously distributed throughout the trabeculae than the osteocytes in age-matched controls (Fig. 6-19). Osteoclasts appear morphologically normal but are increased in number compared with those in individuals not affected by OI.

OI is not one disease; it is a collection of syndromes having in common decreased bone density and the propensity to fracture. From an anatomic viewpoint, three levels of organization may be considered in patients with OI: genetic cellular defects, tissue abnormalities, and structural skeletal abnormalities.

Although only limited information is available relating to cellular defects in OI, both genetic and biochemical evidence indicate that these diseases result from various disorders in collagen synthesis, both quantitative and qualitative.

More information is available concerning tissue abnormalities. The increased number of osteoblasts and osteoclasts, the large size of the osteoblasts, and the greater amount of osteoid-covered surfaces suggest an increase in bone turnover, and this is supported by microscopic studies including increased tetracycline labeling. One of the most characteristic histologic features in OI is the apparent abundance of osteocytes. The quantity of extracellular matrix separating the cells is reduced, and as a consequence, the cells are much closer together. This finding is present in both woven and lamellar bone, suggesting a decrease in the amount of collagen matrix produced by each osteoblast before it becomes an osteocyte. The diminution in the size of the skeleton in OI can be
attributed, at least in part, to this absolute decrease in extracellular matrix production, particularly of collagen. The fact that the lamellae appear unusually delicate and thin is in accordance with this interpretation.

In those patients the author has been able to study at necropsy, two processes were found to affect the epiphyseal ends of the bone. First, a failure in the normal development of the secondary center of ossification results in residual islands of cartilage in the epiphysis (this process was present in most of the epiphyses examined). Second, disruption of the epiphyseal growth plate, which often leaves only irregular islands of growth plate cartilage in the metaphyseal region. A radiographic survey showed that the most severe disruption and fragmentation of the growth plate occurred in the distal femur.

EHLERS-DANLOS SYNDROME

EDS is relatively rare, but it has been described in all races and both sexes. The disease is named after Edward Ehlers of Denmark, and Henri Alexandre Danlos of France. Like OI, EDS, which gives rise to the ‘India rubber man’ of the circus, comprises a group of heterogeneous connective tissue disorders that have only recently been classified into six different types (Table 6-3). In most cases the underlying defect in the pathway of collagen synthesis is unknown.
However, some cases of EDS (kyphoscoliosis type), have demonstrated a hydroxylysine-deficient collagen, probably due to a lysyl hydroxylase deficiency that interferes with the formation of intramolecular cross-links in type I collagen. In the rare disease dermatosparaxis, the disease is caused by a lack of procollagen peptidase. Thus, the conversion of procollagen to collagen is interfered with and the formation of collagen fibrils cannot proceed normally.

Mutations in the ADAMTS2, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, PLOD1, and TNXB genes have been implicated.

The characteristic clinical features of EDS are hyperextensibility of the skin; easy bruisibility; hypermobile joints, which are prone to dislocation; and, in type IV disease, dissecting aortic aneurysm. Blue sclerae are not uncommon in EDS, and their presence should not be taken as evidence of an associated OI. Arthritis is common.

In general, the bone is found on gross examination to be osteopenic (Fig. 6-20). Many patients exhibit a greater or lesser degree of kyphoscoliosis, which becomes worse during adolescence and may end in severe spinal curvature with pulmonary embarrassment (Fig. 6-21). Occasionally, severe spondylolisthesis is observed. No characteristic microscopic findings have been described in the bone.

**SCURVY**

Scurvy, an acquired collagen deficiency disease, is now an extremely rare condition, although an occasional case may arise as the result either of starvation or of food faddism. In the past, when infantile scurvy was common, the childhood disorder was frequently found to be associated with rickets. The adult form was most commonly seen in sailors.

Scurvy is characterized clinically by hemorrhage secondary to capillary fragility. The hemorrhages occur in the skin, gums, muscle attachments, serosal membranes, and especially in children, subperiosteally in the bones (Fig. 6-22). Affected individuals may also exhibit anemia, osteoporosis, intra-articular hemorrhages, and poor wound healing.

The recognition that scurvy is a deficiency state occurred in the late 18th century, when it became understood that the disease resulted from a lack of vegetables and fruit in the diet and that citrus fruit could prevent its onset. It is now known to be caused by a deficiency of ascorbic acid (vitamin C), an essential cofactor for hydroxylation of the amino acids proline and lysine, an important step in the intracellular synthesis of collagen. In the absence of vita-

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**TABLE 6-3 Ehlers-Danlos Syndrome Classification**

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Affects approximately 2 to 5 in 100,000 people. Hypermobility type, symptoms often include unstable, flexible joints with a painful tendency to dislocate and subluxate. This variant is characterized by soft, highly elastic, velvety skin that may tear, bruise, or scar easily or be slow to heal, and that has a tendency to develop benign fatty growths as well as benign fibrous growths on pressure areas. Pregnancy can be life-threatening in this variant. It affects type V collagen as well as type I.</td>
<td>COL5A1, COL5A2, COL1A1</td>
</tr>
<tr>
<td>Hypermobility</td>
<td>Affects 1 in 10,000 to 15,000 and an autosomal dominant trait; it is the only type of EDS that cannot be diagnosed through skin/tissue samples but is rather diagnosed by clinical observations. Symptoms include easy bruising, velvety-smooth skin, mildly hyperextensible skin, and loose, unstable joints. Joint dislocations and subluxations are common. Degenerative joint disease can occur. Some individuals have mitral valve prolapse.</td>
<td>COL3A1, TNXB</td>
</tr>
<tr>
<td>Vascular</td>
<td>An autosomal dominant defect in the type 3 collagen synthesis. It is clinically serious. Hypermobility is usually limited to the fingers or toes, but the delicate skin is joined by fragile blood vessel walls and organ membranes, with a tendency to rupture or develop aneurysms.</td>
<td>COL3A1</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>An autosomal recessive defect due to deficiency of an enzyme called lysyl hydroxylase; it is very rare, with fewer than 60 cases reported. Symptoms include progressive scoliosis, progressive severe weakness of muscles, and fragile sclera.</td>
<td>PLOD1</td>
</tr>
<tr>
<td>Arthrochalasis</td>
<td>Very rare, with about 30 cases reported. This variant may result in very loose and unstable joints, including the hips, which may lead to early or severe osteoarthritis and fractures, and stretchy, fragile skin. It affects type I collagen.</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>Very rare, with few cases reported. This variant combines the loose and unstable joints with extremely fragile skin that loses elasticity.</td>
<td>ADAMTS2</td>
</tr>
</tbody>
</table>

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**Figure 6-20** Photograph of an autopsy section through the femur of a young man with Ehlers-Danlos syndrome shows a healed intertrochanteric fracture and severe osteoporosis.
min C, the conversion of proline and lysine to hydroxyproline and hydroxylysine cannot take place, with a resulting failure in the formation of intramolecular bonds necessary to a stable triple-helical collagen molecule.

In the vitamin C-deficient state, microscopic examination reveals that recently formed areas of connective tissue (e.g., the metaphysis in a growing child) are markedly deficient in extracellular matrix formation. Indeed, the most prominent features in these areas are proliferating fibroblasts without significant collagen production and extravasated red blood cells as a result of failure to form new capillaries (Fig. 6-23).

In young children with scurvy, the bone lesions are characterized by subperiosteal hemorrhage that may be massive (Fig. 6-24).

Marfan's syndrome is an autosomal dominant genetic disorder of connective tissue. Affected individuals are usually tall and thin, with osteopenia, kyphoscoliosis, arachnodactyly, myopia, and often lens dislocation (Fig. 6-26). From a clinical standpoint, the most important aspects of the disease are cardiovascular abnormalities, particularly affecting the heart valves and the aorta. Other affected organs include the lungs and dural ectasia.

Microscopic examination of the heart valves and large arteries reveals a cystic necrosis of the media with pools of mucoid material that stains metachromatically with toluidine blue (Figs. 6-27 and 6-28).

Marfan's syndrome is believed to be caused by mutations in the FBN1 gene on chromosome 15, which encodes a glycoprotein called fibrillin-1, a component of the extracellular matrix. The fibrillin-1 protein is essential for the proper formation of the extracellular matrix including the biogenesis and maintenance of elastin fibers. The extracellular matrix is critical for both the structural integrity of connective tissue but also serves as a reservoir for growth factors. Elastin fibers are found throughout the body but are particularly abundant in aorta; ligaments, especially the ligamentum flavum, hence the spinal deformity; and the ciliary zonules of the eye; consequently these areas are among the worst affected.

Other rare disorders that have similar signs and symptoms to those of Marfan's syndrome and EDS include

- Congenital contractual arachnodactyly (Beals' syndrome)
- Homocystinuria
- Loeys-Dietz syndrome
- MASS (mitral valve, aorta, skin, skeletal) phenotype
- Stickler's syndrome.

In addition, because the primary spongiosa beneath the growth plate fails to form adequately, a fracture through the metaphysis frequently occurs, with a resulting separation of the epiphysis (Fig. 6-25). These metaphyseal fractures are clinically manifested by marked costochondral tenderness and swelling around the major joints. (Because the periosteum is more securely attached to the bone in adults, subperiosteal hematomas are less characteristic. However, adult patients may present with bleeding gums and bleeding elsewhere as well as marked osteoporosis due to the defect in collagen synthesis.)
The nonfibrillar amorphous component of the extracellular tissue matrix is particularly prominent in cartilage and plays an important role in its mechanical properties.

The principal nonfibrillary constituents of cartilage are glycosaminoglycans, which, combined with proteins, form the PG (see Chapter 1).

The mucopolysaccharidoses constitute a group of inborn errors of metabolism, which result from diminished activity of the lysosomal enzymes that degrade glycosaminoglycans (i.e., mucopolysaccharides). At least 11 distinct single lysosomal enzyme deficiencies are known to result in seven recognized phenotypes. These conditions are inherited in an autosomal recessive fashion with the exception of Hunter’s disease. They are characterized by defects in the metabolism, storage, and excretion of these glycosaminoglycans. The majority of these diseases are associated with marked skeletal abnormalities, probably because the glycosaminoglycans are so important in the formation of the early cartilaginous skeleton and its subsequent endochondral ossification during development (Fig. 6-29).

Most of these conditions are characterized by the storage of dermatan sulfate and heparan sulfate in various tissues (Table 6-4). Strikingly affected are the reticuloendothelial system, the heart (Fig. 6-30), and the central nervous system, the latter often resulting in severe mental retardation. Because of the important role played by the glycosaminoglycans in the formation of the vitreous humor and other components of the eye, disturbed vision and blindness is a common complication.

The two most common mucopolysaccharidoses associated with severe skeletal abnormalities are Morquio’s syndrome (MPS IV) and Hunter’s syndrome (MPS I).

**MORQUIO’S SYNDROME**

Morquio’s syndrome (mucopolysaccharidosis IV A and B) is characterized by defective degradation of keratan sulfate, by either N-acetyl galactosamine-6-sulfate sulfatase (GALNS gene) deficiency in MPS
FIGURE 6-26  A, The hands of an adolescent girl with Marfan’s syndrome show the typical elongated fingers (arachnodactyly) associated with the syndrome.  B, Radiograph of the hand.  C, Anteroposterior radiograph of the trunk of the same patient demonstrates the severity of the spinal deformity. (Courtesy of Dr. David Levine.)

FIGURE 6-27  Photomicrograph of a portion of the wall of the aorta, demonstrating pools of mucoid material. The patient died of a dissecting aneurysm, a common complication in Marfan’s syndrome (H&E, × 4 obj.).

FIGURE 6-28  Photomicrograph of a section of the aorta from a patient with Marfan’s syndrome stained to demonstrate the sparsity of elastic tissue (black). Especially in the areas of mucoid degeneration contributing to weakness in the media and subsequent dissecting aneurysm (Verhoeff–van Gieson, × 4 obj.).
IV A or beta-galactosidase (GLB1 gene) deficiency in MPS IV B, and by excessive amounts of keratin sulfate and chondroitin sulfate in the urine. Affected patients are dwarfed, with characteristically flat vertebrae and some vertebral wedging, epiphyseal dysplasia, and generalized osteoporosis. There is usually marked shortening of the trunk with kyphosis and somewhat lesser shortening of the extremities, with genu valgus (Figs. 6-31 to 6-33). Odontoid hypoplasia may occur and is a critical feature to be recognized. Unlike the other type of MPS, Morquio’s patients do not have coarse facial features or mental retardation.

<table>
<thead>
<tr>
<th>MPS Type</th>
<th>Eponym</th>
<th>Deficient Enzyme</th>
<th>Neurodegeneration</th>
<th>Somatic Features*</th>
<th>Corneal Clouding</th>
<th>Bone/Joint Abnormality</th>
<th>MPS Stored†</th>
</tr>
</thead>
<tbody>
<tr>
<td>I H</td>
<td>Hurler</td>
<td>α-iduronidase</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>DS, HS</td>
</tr>
<tr>
<td>I H/S</td>
<td>Hurler-Scheie</td>
<td>α-iduronidase</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>DS, HS</td>
</tr>
<tr>
<td>I S</td>
<td>Scheie</td>
<td>α-iduronidase</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>DS, HS</td>
</tr>
<tr>
<td>II</td>
<td>Hunter</td>
<td>Iduronidase sulfatase</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>DS, HS</td>
</tr>
<tr>
<td>III</td>
<td>Sanfilippo A</td>
<td>Heparan sulfatase</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>HS</td>
</tr>
<tr>
<td></td>
<td>Sanfilippo B</td>
<td>N-acetylgalcosaminidase</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>HS</td>
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<tr>
<td></td>
<td>Sanfilippo C</td>
<td>Acetyl CoA glucosamine acetyltransferase</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>HS</td>
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<tr>
<td></td>
<td>Sanfilippo D</td>
<td>N-acetylgalcosamine-6-sulfatase</td>
<td>+++</td>
<td>+</td>
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<td>HS</td>
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<tr>
<td>IV</td>
<td>Morquio A</td>
<td>Galactosamin-6-sulfatase</td>
<td>–</td>
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<td>KS, CS</td>
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<td></td>
<td>Morquio B</td>
<td>β-galactosidase</td>
<td>–</td>
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<td>KS</td>
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<tr>
<td>VI</td>
<td>Maroteaux-Lamy</td>
<td>N-acetylhexasamine-4-sulfatase</td>
<td>–</td>
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<td>VII</td>
<td>Sly*</td>
<td>β-glucuronidase</td>
<td>–</td>
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<td>DS, HS, CS</td>
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<tr>
<td>IX</td>
<td>Hyaluronidase deficiency†</td>
<td>Hyaluronidase</td>
<td>–</td>
<td>–</td>
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<td>+</td>
<td>Hyaluron</td>
</tr>
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* MPS stored: CS, chondroitin sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate.
* Somatic features: organomegaly, facial coarsening.
† Extreme variability in severity.
‡ Only one patient has been described.
Hurler’s syndrome is marked by progressive mental deterioration, hepatosplenomegaly, dwarfism, and gargoyle-like faces. Affected children may be large at birth and appear normal but may have inguinal or umbilical hernias. Growth in height may be initially faster than normal, then begins to slow before the end of the first year and often ends around age 3, resulting in a maximum stature of less than 4 feet. Distinct facial features including flat face, depressed nasal bridge, and bulging forehead become evident in the second year. The liver, spleen, and heart are usually enlarged. Children with Hurler’s syndrome often die before age 10 from obstructive airway disease, respiratory infections, or cardiac complications.

Although the vertebral bodies appear relatively normal, these patients frequently exhibit a kyphotic deformity resulting from the malformation of at least one vertebral body, usually the twelfth thoracic or the first lumbar (Fig. 6-34). For unknown reasons, a portion of the anterior half of the affected body or bodies fails to ossify,
and the ensuing posterior displacement of one vertebral body on the other leads to kyphosis. However, in Hurler’s syndrome, the vertebral column does not show the general wedging of the vertebral bodies present in Morquio’s syndrome.

### Disturbances in Mineral Formation

**HYPOPHOSPHATASIA (PHOSPHOETHANOLAMINuria)**

Hypophosphatasia is a rare autosomal recessive, genetically transmitted error of metabolism in which there is a deficiency in the synthesis of the enzyme alkaline phosphatase and, therefore, defective bone mineralization. Five forms of the disease have been described: perinatal, infantile, childhood, adult, and odontohypophosphatasia. Perinatal hypophosphatasia is invariably lethal whereas infantile hypophosphatasia has a roughly 50% mortality rate, with symptoms appearing within the first 6 months after birth. These forms of the disease are inherited as an autosomal recessive trait.

In infants, the disease is manifested clinically as a failure to thrive with growth retardation and is accompanied by a wide range of symptoms including irritability, fever, and vomiting. In general, infants diagnosed before 6 months of age follow a rapidly progressive fatal course.

In older children or adults, the disease is less severe, inherited as an autosomal recessive trait, and usually asymptomatic though there may be a history of premature loss of teeth. Hypophosphatasia is characterized by decreased levels of alkaline phosphatase in bones, intestines, liver, and kidneys. Levels of serum phosphorus and calcium are usually at the upper limits of normal. Increased amounts of phosphoethanolamine, which is believed to be a substrate of alkaline phosphatase, are present in the urine and in the serum, and levels of inorganic pyrophosphate are also elevated.

Radiographic manifestations of the disorder in children include poorly ossified and underdeveloped bones (Figs. 6-35 and 6-36). Gross and microscopic examination of the affected tissue reveals increased osteoid and irregular epiphyseal cartilage with lengthened chondrocyte columns (Figs. 6-37 to 6-41). The similarity to rickets is evident and explains why this disease was named vitamin D–resistant rickets for years (see Chapter 8).

Hypophosphatasia may not present clinically until the fourth, fifth, or sixth decade of life, although there is often a childhood history of a rickets-like disorder. Edentia, short stature, and deformity of the extremities, including bowing, are common clinical findings. Radiographic features include pseudofractures and osteopenia. Histopathologic examination of bone from these patients reveals an osteomalacic picture, with increased amounts of nonmineralized
bone. Unlike osteomalacia due to vitamin D or calcium deficiency, hypophosphatasia is characterized by a paucity of osteoblasts.

The topic of hyperphosphatasia will be discussed in Chapter 7 under juvenile Paget’s disease.

**FLUOROSIS**

With excess fluoride in the diet, the fluoride may substitute for some of the hydroxyl ion in hydroxyapatite to form a more stable crystal, fluorapatite, which is less soluble (i.e., less metabolically available) than hydroxyapatite.

Normal adult serum fluoride ranges from 0.5 to 2.3 µM; lowest values are seen in young adults, and levels progressively increase with age to reach peak values of 2 µM in the sixth to eighth decades.

Fluoride intoxication may result from either industrial or endemic exposure to fluoride. In populations exposed to a high fluoride content in water (in excess of 24 parts per 1,000,000), or in individuals exposed to high levels of industrial fluoride, the most dramatic radiographic change is marked coarsening and thickening of bone trabeculae, particularly involving the axial skeleton. Eventually, there is a significant increase in bone density, sometimes accompanied by periosteal new bone formation and marked spinal osteophytosis. There is a propensity for calcification and ossification of the muscles, ligaments, and tendons at the site of their attachment to the bone. Some patients in whom bone formation is particularly prominent in and around joints may develop debilitating arthrosis. Affected individuals may also exhibit mottled tooth enamel and anemia.

**FIGURE 6-38** Hypophosphatasia: low-power photomicrograph of the upper femoral growth plate. The marked irregularity of the cartilage and the tongue of irregular cartilage extending to the metaphyseal region are evident (H&E, ×1 obj.).

**FIGURE 6-39** Photomicrograph to demonstrate a normal upper femoral epiphysis to show the difference in a patient of the same age as the subject of Figure 6-38 (H&E, ×1 obj.).

**FIGURE 6-40** Photomicrograph of a cross-section of a growth plate in hypophosphatasia demonstrates disturbed endochondral ossification (H&E, ×10 obj.).
In recent years, fluoride has been used to stimulate bone production in osteoporotic patients. Fluoride in doses of approximately 20 to 30 mg of elemental fluoride daily to achieve a serum level of approximately 10 µM may result in increased bone density in some subjects (Fig. 6-42). However, its usefulness as a mode of treatment has been questioned.

Microscopic examination of the sclerotic fluorotic bone in treated patients reveals it to be predominantly lamellar, although with increased osteocytes that themselves do not appear normal; the matrix frequently shows basophilic mottling around the osteocytic lacunae or enlargement of the lacunae themselves. An increased amount of osteoid as well as increased cement lines are also present (Figs. 6-43 to 6-45). A marked increase in the diameter of the cortical haversian systems may give a spongy appearance to the cortex.

**Dwarfism (Chondro-osseous Dysplasia)**

Many of the diseases discussed in this chapter result in a stunting of growth that is sometimes dramatic, as in OI and the various mucopolysaccharidoses, especially Morquio’s syndrome.

Dwarfism may also be caused by defects in the epiphysis or in the growth plate, either from a lack of those extrinsic factors necessary for cartilage growth, as occurs with deficiency of growth hormone (pituitary dwarfs), or from cellular deficiencies in the chondrocytes that might interfere with endochondral ossification, such as appears to be the case with achondroplasia (Figs. 6-46 to 6-48). Although many different clinical syndromes have been described, mostly by radiologists, for the most part the underlying molecular defects remain unknown.
Radiographic classification of these conditions is based either on the portion of the long bone (epiphysis, metaphysis, or diaphysis) most obviously involved, and on the presence or absence of spinal involvement; or by the portion of the extremity involved (Fig. 6-49). The age of the patient at the time of presentation (e.g., newborn, infant, child, or adult) is important in categorizing the abnormalities that result in dwarfism.

Proximal shortening or disproportionate shortening of the humerus and femur is known as rhizomelic dwarfism; shortening of the bones of the leg or forearm is known as mesomelic dwarfism; and shortening of small distal parts is known as acromelic dwarfism.
Section III: Metabolic Disturbances

Figure 6-48: Photomicrograph of the growth plate and metaphyseal bone from an achondroplastic dwarf to show the lack of normal maturation and columnation in the growth plate and the presence of a bony end-plate in the metaphysis (H&E, x 2.5 obj.).

Figure 6-49: Radiologic classification of chondrodysplastic dwarfism.
Osteosclerotic Conditions, 162

- Osteopetrosis (Marble Bone Disease, Albers-Schönberg Disease), 162
- Paget’s Disease (Osteitis Deformans), 165
- Rare Forms of Osteosclerosis of Unknown Etiology Both Localized and Generalized, 173

Osteopenic Conditions, 175

- Generalized Osteoporosis, 175
- Localized (Transient) Osteoporosis, 183
- Idiopathic Osteolysis, 185
Like most tissues of the body, the bony skeleton is in a continuous state of formation and breakdown, enabling it to constantly adapt to the environment, especially the mechanical demands. For the amount of bone tissue to remain the same, there must be a balance between formation of the extracellular matrix by the osteoblasts and its breakdown by the osteoclasts, processes regulated by both local and systemic factors (see Chapter 1, Tables 1-2 and 1-3). Any disturbance in the linkage between these two processes will result in either a decrease in bone density (osteopenia) or an increase in bone density (osteosclerosis) (Fig. 7-1). In general, because disturbed skeletal homeostasis is not the result of disturbances of calcium homeostasis, the blood calcium levels are essentially normal.

### Osteosclerotic Conditions

Localized increased radiographic density is a relatively common finding in the skeleton, and is usually associated with metastatic cancer or, less commonly, primary tumors or marrow disease, such as lymphoma or myelofibrosis. What follows will focus on sclerosis, either localized or generalized, which is due to disturbed cell linkage, and mainly on osteopetrosis and Paget’s disease, in both of which osteoblast dysfunction appears to be the problem.

#### Osteopetrosis (Marble Bone Disease, Albers-Schönberg Disease)

Osteopetrosis is a rare heterogeneous group of heritable disorders characterized by a marked increase in the density of the bones. The bones are generally short and frequently exhibit a modeling defect characterized by loss of the normal metaphyseal flare, sometimes referred to as an Erlenmeyer flask deformity (Fig. 7-2). This deformity is most prominent in the areas of rapid growth, that is, the lower femur, upper tibia, and upper humerus. (A similar deformity may also be seen with Gaucher’s disease [see Chapter 9].) Osteopetrosis is often complicated both by multiple fractures resulting from a disturbed microarchitecture (Fig. 7-3) and by anemia resulting from the marked reduction in the marrow space (Fig. 7-4).

Three clinical presentations have been recognized. In the severe (malignant) form that usually causes death in utero or in early infancy, it is inherited as an autosomal recessive trait. In this severe form of the disease, marrow cavities fail to develop, leading to extramedullary hematopoiesis, anemia, leukoerythroblastosis, and progressive hypersplenism. Obstruction of the cranial foramina results in increased intracranial pressure, optic atrophy, deafness, and cranial nerve palsies. Development is progressively impaired in these children, and death usually occurs during the first years of life from anemia, bleeding, or infection.

There are two less severe (benign) forms of the disease in which the patients live into adult life; one is also inherited as an autosomal recessive condition and the other as an autosomal dominant condition. In the latter form, diagnosis may be delayed until late middle age, when the disease usually presents because of a pathologic fracture or as an incidental radiologic finding. In such a case, the condition must be differentiated from other causes of increased bone density, such as widespread osteoblastic metastases or myelosclerosis.

In severely affected patients, radiologic examination of the skeleton may reveal a uniform opacity of the skeletal tissue, with loss of the usual corticomedullary demarcation (Fig. 7-5). However, in less
severely affected patients, it is not unusual to find, particularly in the pelvis and the peripheral bones, alternating areas of affected and apparently normal bone, which give a peculiar striped appearance to the radiographic image (Fig. 7-6). In the vertebral bodies, a central, horizontal lytic stripe is often seen, which gives the vertebrae a sandwich-like appearance (Fig. 7-7). Occasionally, spinal involvement may give rise to a lumbar spondylolisthesis because of fractures through the pars interarticularis.

Gross examination of the bones obtained from fatal infantile cases shows widening in the region of the metaphysis and diaphysis (the characteristic Erlenmeyer flask deformity). The affected bones have increased density, and despite the fact that they are usually somewhat smaller than normal, may weigh two to three times more than normal bone. On sectioning, the bone tissue is generally very hard and compact, with complete loss of the normal cancellous architecture (Figs. 7-8 and 7-9).

Microscopic examination reveals extremely dense and irregular bone trabeculae, nearly all of which have a central core of cartilage (Fig. 7-10). (Compare with the primary spongiosa that normally forms in the metaphysis during development, which has a similar appearance but is rapidly remodeled to the adult form of bone [Chapter 1]. In patients with osteopetrosis, the mechanism by which

FIGURE 7-3 Multiple fractures of the forearm and elbow are demonstrated in this young patient with osteopetrosis. Although the bone is denser than normal, it is less strong because of its disturbed microarchitecture. Note the transverse direction of the fractures (banana fracture).

FIGURE 7-4 Osteopetrosis: gross appearance of two resected vertebral bodies in frontal section (A) and a radiograph of these vertebrae (B). The obliteration of the marrow space results in extramedullary hematopoiesis.

FIGURE 7-5 Radiograph of the upper body of a child with osteopetrosis. A marked increase in density of all the bones is apparent.
this remodeling is effected appears to be deficient, and the primary spongiosa together with its cartilage core therefore persists.) Although a paucity of osteoclasts has sometimes been reported in patients with osteopetrosis, in many cases, microscopic examination shows abundant osteoclasts. However, microscopic studies have demonstrated that, at least in some cases, these osteoclasts lack ruffled borders and that although the cells are in proximity to the bone and calcified cartilage, they do not show the cytologic features normally present in an active osteoclast (Fig. 7-11). In other words, although osteoclasts are present, they do not appear to be functioning normally.

Three mutations linked to osteopetrosis cause defects in osteoclast function: carbonic anhydrase II deficiency, osteoclast proton pump deficiency, and defects in the chloride channel. The most common of these, found in 50% to 60% of patients, results from defects the osteoclast vacuolar H^+-ATPase proton pump. The most obvious microscopic defect is the failure to resorb calcified cartilage, and it is perhaps here that the osteoclasts are most deficient.

**FIGURE 7-6** Clinical radiograph of the hands of an adult patient with osteopetrosis. The proximal end of the first metacarpal clearly shows alternating stripes of dense involved bone, with less dense and apparently normal bone distally.

**FIGURE 7-7** In this adult patient with osteopetrosis, the spine shows markedly increased density of the proximal and distal thirds of the vertebral bodies, giving a sandwich-like appearance.

**FIGURE 7-8** Radiograph of the thighs in a child with osteopetrosis shows a lack of metaphyseal remodeling, which gives rise to an Erlenmeyer flask deformity. Normal cortical medullary differentiation is not seen, and the bones are strikingly dense. Again a striped appearance is seen in the distal femoral metaphysis.

**FIGURE 7-9** Gross appearances of a femur removed from a child with osteopetrosis seen in frontal (A) and cut section (B). Note the characteristic Erlenmeyer flask deformity of the distal end of the femur and uniform density of the bone in the cut section.
It should be noted that a percentage of patients with osteopetrosis as yet have no identifiable gene defect.

In osteopetrotic mice, restoration of normal bone and cartilage resorption has followed the transplantation of normal bone marrow or spleen cells. This procedure has also been tried in humans with some promise of success.

**FIGURE 7-10** A. Photomicrograph demonstrates residual cartilage in an adult patient with osteopetrosis. B. The same field has been photographed using polarized light, which clearly differentiates the bone and calcified cartilage (H&E, × 4 obj.).

**FIGURE 7-11** Histologic section taken from a young child with osteopetrosis, showing numerous osteoclasts in the tissue. However, these osteoclasts do not seem to be resorbing bone (H&E, × 10 obj.).

**PAGET’S DISEASE (OSTEITIS DEFORMANS)**

In November 1876, Paget, in a paper read to the Royal Medical and Surgery Society, described the disease that now universally bears his name. He was 62 years old.

The case that he described was that of a military gentleman who had been his patient for more than 20 years and eventually had died of a malignancy in the radius. When the patient had been first seen, it was because of deformity in the left tibia. Over the next 17 years of his life, the disease continued to progress slowly. The left femur and tibia became larger, heavier, and somewhat more curved. Very slowly the bones of the right limb followed the same course. The skull became gradually larger so that nearly every year his hat needed to be enlarged. From a height of 6'1 he sank to about 5’9. The attitude in standing was described as looking simian, “strangely in contrast with the large head and handsome features” (Fig. 7-12).

In December, 1872, the patient’s sight was partially destroyed by retinal hemorrhages, first in one eye and then in the other, and at nearly the same time he began to be somewhat deaf. In January, 1876, he began to complain of pain in his left forearm and elbow and swelling appeared about the upper third of the radius and increased rapidly. On 24th March, after 2 days of distress with pleural effusion on the right side, he died, and at autopsy, a malignant tumor was found in the radius.

In most instances, Paget’s disease is localized and maybe only one bone is affected. Because the condition is perhaps most often asymptomatic, it is discovered only accidentally on imaging studies. In the past, when careful autopsies were done, foci of undiagnosed Paget’s disease in the spine or skull were commonly found.

In a patient does present with clinical disease, it is most likely to be either localized discomfort in an extremity or in the back, deformity, the onset of arthritis in the hip or knee, or even pathologic fracture. Rarely the patient may present initially with deaf-
ness or some other neurologic symptom; very rarely a sarcoma (Box 7-1).

Virtually any bone in the body may be involved, but the most common sites are the lumbar spine, pelvis, skull, femur, and tibia. The peripheral skeleton is generally spared (Fig. 7-13). Less commonly, the disease is multifocal or even generalized. Small, incomplete cortical fractures may be numerous, particularly in weight-bearing bones. Progressive bowing of the femoral neck and wedging of the vertebrae are often the result of repeated microfractures, which may progress to complete transverse fractures. However, as shown in Figure 7-14, bowing of the legs may also result purely from bone overgrowth.

Clinical evaluation of patients with Paget’s disease reveals a high incidence of arthritis in the joints adjacent to involved bones. Clinical arthritis is commonly seen in the hip joint, and it is characterized on radiologic examination by concentric joint narrowing (Fig. 7-15). This narrowing appears to result from an accelerated rate of endochondral ossification in the calcified zone of the articular cartilage (consequent to the increased vascularity and turnover of the subchondral bone; see Chapter 10 for further discussion of this phenomenon). Overall increased bone size and deformity, resulting from accelerated bone modeling, also contributes to the arthritic process by altering the load distribution (Fig. 7-16).

The incidence of Paget’s disease varies with ethnicity; although common in Anglo-Saxon northern Europeans including New Zealanders and Australians, it is very rare in blacks and Southeast Asians (with perhaps the exception of Hong Kong and India [both former British colonies]). In large autopsy series in northern Europe, the incidence of Paget’s disease has been reported to be between 3% and 4% of all individuals older than the age of 40 (this probably underestimates the true incidence, which in some localities, may be much higher). In these autopsy studies, the disease was most often limited to a part of the vertebral column or the pelvis (the only parts of the skeleton usually examined at autopsy), and in most subjects, the disease had not been diagnosed during life. Between 15% and 40% of affected individuals have a first-degree relative with the condition, and its familial pattern has long since suggested an inherited pattern.

Recent multicenter molecular genetic studies have suggested that ubiquitin-associated (UBA) domain-specific mutations in the sequestosome 1 (SQSTM1) gene are a contributory cause of both familial and sporadic Paget’s disease.
Electron microscopic observations of the osteoclasts of patients with Paget’s disease have demonstrated the presence of specific intranuclear inclusions composed of microcylinders. These inclusions have also been found in the giant cells of giant cell tumors associated with Paget’s disease and are illustrated in Figure 7-17. The common finding of virus-like inclusions suggested a slow viral disease, and both measles and canine distemper virus have been implicated.

Clinical Laboratory Findings
An elevation of serum alkaline phosphatase activity (in association with the increased osteoblastic activity) to as much as 20 to 30 times the normal level has been recorded. The acid phosphatase level, too, tends to be at its upper limit or even slightly above normal.

The serum calcium and phosphorus levels are ordinarily within normal limits in Paget’s disease. However, hypercalciuria and stone formation is an occasional complication following prolonged bed rest in a patient with extensive bone involvement. Elevated urinary hydroxyproline (or pyridinoline) levels can also be expected as a consequence of increased bone tissue breakdown. Regional blood flow studies have reported increased vascularity, in some instances as much as 20 times normal.

Radiologic and Gross Features
The radiologic appearance of Paget’s disease is variable. In the earliest stages, during which osteoclastic resorption predominates, there is a striking radiolucency without any thickening of the bone; in the skull, this has been called osteoporosis circumscripta (Fig. 7-18). In the later stages of the disease, when resorption diminishes, the overall density of the bone increases (Fig. 7-19). The trabeculae or the cancellous bone can be seen to become thicker, coarser, and more irregular. On the other hand, the cortical bone becomes less compact and there is loss of corticomedullary demarcation (Figs. 7-20 and 7-21). The periosteal and endosteal surfaces become rough and
irregular rather than smooth, and there is usually an increase in the diameter of the affected bone.

Radiologic examination of the vertebral bodies may reveal either uniformly increased radiodensity suggestive of lymphoma or metastatic tumor or, more commonly, a ‘picture frame’ appearance (Figs. 7-22 to 7-24). In the pelvis, it is common to find combinations of increased density and lytic areas, as well as areas with a honeycombed or striated appearance.

In long bones, the process usually starts at one end, occasionally both, and spreads toward the center. The junction between the normal and diseased bone is demarcated as an advancing wedge of rarefaction frequently described as flame like (Figs. 7-25 and 7-26).

In long bones, the early phase of the disease may on occasion be mistaken for a tumor, especially when the diagnosis of Paget’s is not considered because of the patient’s age (Fig. 7-27).

In scintigraphic studies, isotope uptake is increased at all stages of the disease (Fig. 7-28). The radiologic diagnosis in established disease should not be difficult, but in those instances in which the disease process is limited, it can be, especially in those cases in which metastatic cancer is suspected (Fig. 7-29).

**Microscopic Appearance**

Just as with the radiologic appearance, the microscopic appearance depends on the stage of the disease process. It may be divided into three phases. The early acute phase of the disease is characterized by
large numbers of multinucleate giant osteoclasts, often with 10 to 20 nuclei that can be seen to be rapidly removing mature bone tissue, whereas in other areas, swollen osteoblasts with prominent Golgi apparatus, giving them a plasmacytoid appearance, are laying down immature woven bone. The marrow spaces are hypervascular with a cellular and loose fibrillary stroma. Inflammatory cells are absent.

The microscopic picture is one of frenetic cell activity, which may be impossible to differentiate from hyperparathyroidism (Fig. 7-30). However, in most cases, the two conditions may be differentiated because in Paget’s disease, the osteoclasts are generally bigger, with more than 10 to 20 nuclei, and in hyperparathyroidism, there is tunneling resorption (see Chapter 8 on hyperparathyroidism).
This initial, mainly destructive phase is followed by an osteoblastic phase in which new bone formation predominates over resorption. Massive trabecular plates are built up to a density that is neither cortical nor cancellous in its architecture. The increased rate of bone formation and bone resorption results in an increased number of reversal fronts or cement lines, which, in turn, gives rise to the classic ‘mosaic pattern’ (Fig. 7-31). However, the recognition of the mosaic pattern depends upon the quality of staining, and it may be easily overlooked unless one routinely uses polarized light for the microscopic examination of bone (Fig. 7-32).

The alteration in microarchitecture, together with the increased number of cement lines, leads to structural weakness in the tissue and facilitates the propagation of cracks. Again, studies of the orientation of the collagen in bone by polarized light microscopy reveal the discordant nature of the new structure, which may not be so apparent without it.

A final ‘burnt out’ phase is generally described, during which cell activity is less intense and vascularity diminished. The microscopic picture is that of heavily trabeculated bone showing a prominent mosaic pattern. However, the turnover rate of the diseased bone may not be much greater than that of normal bone, and in this late stage, the marrow may have a relatively normal appearance (Fig. 7-33).

In 1981, Wick and his associates reported the Mayo Clinic experience of malignant degeneration: out of about 4000 patients clinically diagnosed with Paget’s disease over a 50-year period, there were about 38 cases of complicating primary malignant bone tumors (or 0.95%), the pelvis, humerus, and femur being the most common sites (Figs. 7-34 and 7-35). The sarcoma that develops usually shows a mixed pattern of osteosarcoma, fibrosarcoma, chondrosarcoma, and malignant histiocytoma; that is, a mixed mesenchymal pattern. Sarcoma is a complication not only of widespread disease but rarely it may be engrafted on monostotic Paget’s disease (Fig. 7-36).

Giant cell tumors (GCTs) may very rarely complicate Paget’s disease and may be multifocal. Unlike conventional giant cell tumors, they appear in the skull, facial bone, and spine (Fig. 7-37). Although these tumors appear similar to GCTs, it has been suggested that they may be reactive lesions like the “brown tumors” of hyperparathyroidism.

Paget’s disease may also be complicated by other tumors either metastatic or primary. Myeloma, lymphoma, and metastatic cancer
have all been reported in association with Paget's disease, and may on occasion need to be differentiated from Paget's sarcoma. Pseudosarcomatous lesions, in some cases characterized by florid new bone and abundant periosteal bone formation, have also been described (Fig. 7-38), further emphasizing the need for biopsy in cases where tumor is suspected, both for accurate diagnosis and so that treatment can be appropriate.

**Juvenile Paget's Disease**

Primary hyperphosphatasia, also known as juvenile Paget's disease, is a rare congenital autosomal recessive disorder caused by mutations in TNFRSF11B (tumor necrosis factor receptor super family 11B) encoding osteoprotegerin. The disease is characterized clinically by short stature, a propensity to fracture, and marked subperiosteal bone formation, which may be confused with Caffey’s disease (see Chapter 5). Patients with this condition have markedly elevated levels of serum alkaline phosphatase and acid phosphatase of bone origin, and an elevated level of urinary hydroxyproline.
On radiographic examination, a thickened skull with ‘cotton ball’ radiodensities may be seen. The long bones often exhibit an increase in width and loss of normal corticomedullary differentiation. These features are the result of the marked subperiosteal overgrowth. Bowing due to fractures may be present (Fig. 7-39).

Morphologic studies reveal that both the cortical and trabecular bone consists of immature or woven bone, with abundant osteoblasts and osteoclasts and prominent osteoid seams. The marrow space is replaced by a well-vascularized fibrous connective tissue network. Using polarized light, a mosaic pattern of the bone matrix can be observed.

FIGURE 7-25—CONT’D B. Gross photograph. C, Histologic section of the advancing edge of involved bone—note the involved fibrotic and pagetic bone eroding the normal bone cortex (H&E, x 2.5 obj.).

FIGURE 7-26 In this lateral radiograph of the leg of a 55-year-old woman with Paget’s disease of the distal tibia, an obvious junction is seen between the involved cortex and the noninvolved cortex, where there is a flame-like or wedged outline. (Courtesy of Dr. Alex Norman.)

FIGURE 7-27 Radiograph and isotope scan of the forearm of a 25-year-old woman who suffered a fracture of the radius after lifting her 3-year-old son. The diffuse demineralization and altered trabecular pattern resulted in a differential diagnosis that included round cell tumor, infection, and adamantinoma. A biopsy showed this to be Paget’s disease (<4% of individuals with Paget’s present younger than age 40 years). (Courtesy of Dr. Howard Dorfman.)
Hyperphosphatasia is distinguished clinically from Paget’s disease by its early onset and the generalized symmetric bone involvement.

RARE FORMS OF OSSIOSCLEROSIS OF UNKNOWN ETIOLOGY BOTH LOCALIZED AND GENERALIZED

Localized Monomeric Medullary Osteosclerosis

This rare entity has been most often reported in the leg. The patients presented with mild to moderate pain in lower extremity that was made worse by exercise. The pain was accompanied in some cases by a feeling of warmth in the affected area. Both children and young adults have been affected. None had a history of infection or trauma. The affected area was generally the middle or lower tibia. Radiographically increased bone density was apparent and isotope studies showed increased uptake. Computed tomography (CT) scans have shown increased medullary density. Biopsy has shown irregular and disorganized woven bone. The condition appears to be nonprogressive (Fig. 7-40).

Camurati-Engelmann Disease (Progressive Diaphyseal Dysplasia)

The clinical features of Camurati-Engelmann disease are painful lower limbs, a waddling gait, and wasting muscles. The disease is usually hereditary, with an autosomal dominant mode of transmission with mutation in the transforming growth factor beta 1 (TGFβ1).
gene. The symptoms usually become manifest early in life, commonly before the age of 10 years. However, occasional cases have been reported in which the patient’s age at diagnosis has been as late as the fifth decade.

The disease is diagnosed primarily on the basis of radiologic examination. Symmetric sclerosis is observed, and often a fusiform enlargement of the diaphysis of the long bones, especially the femur and tibia (Fig. 7-41). The epiphyses are spared. There may also be

**FIGURE 7-31** Photomicrograph demonstrates the thick, irregular plates of bone formed in Paget’s disease. In this section, the basophilic cement lines are clearly seen. Note the microcracks that occur at the site of the cement lines and result in structural weakness (H&E, × 10 obj).

**FIGURE 7-32** A. Histologic features of the late stages of Paget’s disease. It can be difficult to appreciate the mosaic pattern, either because the tissue has been overdecalcified or because the staining is not adequate to show the basophilic lines clearly (H&E, × 10 obj). B. When the same field is examined by polarized light using a first-order red filter, the disorganized pattern of the bone structure is clearly demonstrated.

**FIGURE 7-33** A. Photomicrograph showing a fragment of cancellous bone and cellular bone marrow that at first sight might be passed over as normal. However, when examined using polarized light (B), the discordant arrangement of the collagen fibers should alert the pathologist to the possibility of Paget’s disease (H&E, × 10 obj). C. A higher power photomicrograph to show disorganized pattern and irregular cement lines (H&E, × 25 obj).
changes in the skull, and rarely in the pelvis, mandible, clavicle, ribs, spine, metacarpals, and phalanges (Fig. 7-42).

The disorder is characterized histologically by a thickened cortex, which results mainly from increased endosteal new bone formation. However, periosteal new bone formation is sometimes observed. In children, the enlargement of the cortex of the bone produces a narrowed medullary cavity that, if the narrowing is severe enough, may lead to extramedullary hematopoiesis and eventual hepatosplenomegaly.

The serum chemistries in patients with Camurati-Engelmann disease are usually reported as normal, although an increase in the level of alkaline phosphatase (of bone origin) is sometimes observed.

**Generalized Osteosclerosis of Obscure Etiology**

Very rare cases of generalized osteosclerosis associated with severe and unremitting bone pain have been seen associated with hepatitis C infection. Such a case is illustrated in Figure 7-43.

**Osteopenic Conditions**

**GENERALIZED OSTEOPOROSIS**

Osteoporosis may be defined as low bone mass associated with microarchitectural deterioration of bone tissue leading to enhanced bone fragility and an increase in fracture risk. Decreased mass of the mineralized skeleton (osteopenia) is a nonspecific condition that may result from any of a number of causes, including mineral and collagen disturbances, hematologic and endocrine abnormalities, neoplastic disorders, or immobilization (Table 7-1).

In most people the amount of bone tissue in the skeleton decreases with age (Fig. 7-44). This decrease is more clinically significant in women than in men, and in whites and Asians than in blacks. This is because, in general, men and blacks start out with a higher bone density and also because of the association of increased bone loss with the onset of menopause in a significant number of women.
Figure 7-36  Spinal radiograph (A) of a 58-year-old woman with a 2-month history of low back pain. She had undergone hysterectomy for cervical carcinoma 14 years earlier. A patchy sclerotic and lytic appearance was noted, which was interpreted to be consistent with metastatic disease. However, there was some widening of the body, which is uncharacteristic of metastatic disease. Needle biopsy showed an anaplastic tumor with many giant cells, consistent with Paget’s sarcoma; foci of bone obtained with this biopsy showed the typical mosaic pattern of Paget’s disease. The patient died approximately 4 months later. Autopsy revealed local extension of the tumor, which involved T12 and L2, and compression and encasement of the vena cava. Extensive lung metastases had the pattern of a Paget’s sarcoma. An H&E section (B) of a portion of bone adjacent to the tumor shows increased numbers of cement lines within the bone. In the polarized section (C) of the same field, the disorganized bony architecture is obvious (H&E, × 4 obj.). This case is significant because it demonstrates that even in monostotic Paget’s disease, a sarcoma may rarely occur as a complication.

Figure 7-37  A, Myelogram of the spine in a patient with Paget’s disease (note the irregular coarse density of several vertebral bodies clearly seen in the pedicles). The myelogram shows an occlusion at the level of L1 with displacement of the dura by a soft tissue mass. B, Photomicrograph of tissue obtained from a biopsy of this mass reveals a conventional giant-cell tumor (H&E, × 10 obj.).
It is a remarkable thing that it is only over the past 25 years that osteoporosis has come to be recognized as a major public health threat.

Age-related osteopenia that results in fracture (usually vertebral crush fractures, Colles’ fractures, or femoral neck fractures) is generally referred to as osteoporosis and is twice as common in women than in men. In about a third of women with osteoporosis, it is related to the menopause. These two common types of osteoporosis have been classified by Riggs and his colleagues on the basis of their different clinical findings as type I osteoporosis (postmenopausal) and type II osteoporosis (senile or age related). In postmenopausal osteoporosis, bone loss is rapid and has been associated with increased osteoclastic activity. (It appears that estrogen normally acts as a block to a second messenger from the osteoblast to the osteoclast when the former is stimulated by parathormone. Thus, estrogen deficiency may indirectly increase the sensitivity of the osteoclasts to parathyroid hormone.) In senile osteoporosis, bone loss is slow but relentless, and has been associated both with decreased synthesis of bone matrix by the osteoblasts as well as increased osteoclastic activity (Table 7-2).

It should be recognized that many factors affect bone tissue loss; particularly important are physical activity level and diet. The maintenance of skeletal mass is especially affected by activity levels. Daily weight-bearing activity is essential to the health of the skeleton, and mechanical weight-bearing stress is perhaps the most important exogenous factor affecting bone development and bone modeling. An interesting example of this process has been observed

**FIGURE 7-38** Radiograph of the femur from a patient with Paget’s disease shows an expanded lytic area that seemed to indicate the development of a sarcoma; however, biopsy showed that this area was formed entirely of reactive tissue.

**FIGURE 7-39** A. Radiograph of the skull in an 11-year-old patient with hyperphosphatasia (juvenile Paget’s disease). Note the marked thickening of the calvaria and the ‘cotton ball’ radiodensities throughout. B. Radiograph of the pelvis and upper femurs demonstrates marked thickening of the shafts of the femurs, with bowing of the femur and a dense irregular cortex. C. Photomicrograph of bone biopsy from the patient shown in A and B. The bone is somewhat immature, with large irregular cells. Note prominent cement lines and many osteoblasts on the bone surface (H&E, × 25 obj.).
in astronauts. The marked reduction in gravitational field that results in the weightless environment of space flight leads to profound and rapid loss of skeletal and muscle mass. In everyday experience, a sedentary person is more likely to become osteoporotic than a person who engages in some form of weight-bearing exercise.

An adequate balanced diet is essential, and lack of it is an important contributor to disease. It has been said that the average American woman has a calcium intake of between a third and a half of her total daily requirement. Chronic calcium deficiency in the diet leads to increased secretion of both parathyroid hormone and the hormonally active form of vitamin D, 1,25(OH)2D (see Chapter 8), both of which stimulate osteoclastic activity. Excessive alcohol consumption and smoking also contribute to osteoporosis.

The characteristic radiologic features in patients with osteoporosis are thinning of cortical bone and generalized rarefaction of the skeleton (Fig. 7-45). In postmenopausal osteoporosis, bone loss is mainly of cancellous bone, with less cortical bone loss, whereas in senile, age-related osteoporosis both cancellous and cortical bone loss are present. (As the cortex becomes thinner, the overall diameter of the bone tends to increase to maximize mechanical efficiency.)

In the vertebral column, there is thinning and eventual disappearance of the transverse trabeculae and subsequent thickening of the vertical trabeculae, followed later by the thinning of these trabeculae as well (Fig. 7-46). Compression fractures occur, giving rise to the widening of the intervertebral disc, the so-called “fish-mouth” appearance (Fig. 7-47). In general, the lower thoracic and upper lumbar vertebrae are most affected. Radiologic surveys have shown that about 20% of men and 30% of women older than age 60 have compression fractures of the vertebral bodies. Therefore, back pain associated with loss of height due to vertebral compression and increased thoracic kyphosis are common manifestations.

Bone mass is one of the major determinants of bone strength, and its quantification is predictive of future fracture risk. (In this

**FIGURE 7-40** A, Radiograph of the left leg of a 12-year-old boy who had complained of pain in the leg for 3 weeks. The boy had no systemic symptoms. Temperature, sedimentation rate, and white blood cell count were normal. B, Computed tomography scan shows mineralization of the medullary space. C, Photomicrograph of biopsy material from the medullary space shows woven bone and loose fibrovascular tissue (H&E, x 10 obj.). D, Photomicrograph of the same field shown in C demonstrates a thin layer of lamellar bone covering the woven bone (polarized light microscopy, x 10 obj.).
regard, Carter and Hayes have shown that the compressive strength of trabecular bone is proportional to the square of its apparent density. Thus, if the density decreases by a factor of two, the compressive strength decreases by a factor of four.)

Because vertebral bone loss has to be approximately 30% before it can be radiologically detected, radiologists have long sought special techniques for the evaluation of bone mass, density, and calcium content. Several methods have been widely used for assessing the bone tissue mass based on measurements of bone mineral content, including:

**FIGURE 7-41** Bone scan demonstrates increased diaphyseal uptake over the femurs and tibias bilaterally in a case of hyperostosis generalisata.

**FIGURE 7-42** Radiograph of the hands of a child with Camurati-Engelmann disease illustrates the cortical sclerosis and fusiform enlargement of the metacarpals typical of this disease.

**FIGURE 7-43**

A. Radiograph of a 49-year-old man with a 3-year history of bone pain. Note the markedly thickened, dense cortex, which is more clearly defined than the thickened but sponge-like bone of Paget’s disease. In this patient, the serum calcium and phosphate levels were within normal limits, although the alkaline phosphatase level was persistently elevated (up to 1600 mU/mL). B. Photomicrograph of a cortical biopsy from this patient. Bone surfaces are covered by a thin layer of osteoid, indicating increased bone formation. The endosteal surface (right) appears hypercellular with respect to osteocytes. The bone is lamellar, with no increase in cement lines, differentiating this from Paget’s disease (undecalciﬁed bone, Goldner stain, × 4 obj.). C. Photomicrograph taken at a higher power to demonstrate the prominent osteoblasts lining the endosteal surface of the bone together with a moderately thick layer of unmineralized osteoid (undecalciﬁed section, Goldner stain, × 25 obj.).
Section III: Metabolic Disturbances

1. Single-photon absorptiometry, performed for the assessment of cortical bone in the appendicular skeleton, uses the isotope iodine 125 (125I) as a source of photons, which are then passed through the forearm. The attenuation of the beam is measured by a scintillation counter.

2. Dual x-ray absorptiometry (DXA) was introduced commercially in 1987, and at present, is probably the most widely used system for measuring skeletal mass. With this system, two distinct energy level beams are generated. The preferred anatomic sites for DXA measurement of bone mass include the lumbar spine, proximal femur, and the whole body, but other parts, such as the forearm and calcaneus, can also be scanned. When measuring the spine, it is important to realize that aortic calcification, degenerative arthritis of the spine, or both, may contribute to falsely high readings, as may vertebral compression fractures, where the porosity may be masked owing to compaction of the trabeculae and formation of fracture callus (Fig. 7-48).

3. Quantitative CT scanning (QCT) allows densitometric measurements of cross-sections of a vertebral body, which are then compared with a phantom. Besides its usefulness in measurement of bone mineral density, QCT is an imaging technique that can provide structural information on the regions examined.

One of the problems with measuring local bone mass results from the lack of structural homogeneity, which is dramatically illustrated in a normal vertebral body from a healthy 19-year-old man in Figure 7-49.

Morphometric analyses of standardized bone biopsies allow quantification of the cell parameters, the amount of bone present, and the degree to which osteoid is present on the surfaces of the trabecular and cortical bones have led to the characterization of some of the types of osteoporosis (Fig. 7-50). Although cell activity, that is, relative and absolute osteoblast and osteoclast counts, is usually low in senile osteoporosis, indicating a relatively inactive state, it may sometimes be high. In more than 15% of patients, this increased activity is associated with normocalcemic, normophosphatemic hyperparathyroidism. An additional subgroup of osteoporotic patients is noted to have increased osteoid surfaces (Fig. 7-51). Because this increased osteoid does not seem to be associated with an increased rate of bone formation, it must be related to a mineralization defect, the nature of which is at present unclear. In disuse osteoporosis, the most dramatic initial finding is an increase in the number of resorp-

<table>
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<tr>
<th>TABLE 7-1 Causes of Osteopenia</th>
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<td><strong>Type of Defect</strong></td>
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| Disuse | Prolonged bed rest  
General inactivity  
Prolonged casting or splinting (localized osteoporosis)  
Angiodystrophy (localized osteoporosis)  
Paralysis  
Paraplegia, quadriplegia, hemiplegia, lower motor neuron disease  
Space travel weightlessness |
| Diet | Deficiency of calcium, protein, vitamin C  
Anorexia nervosa |
| Drugs | Heparin  
Methotrexate  
Ethanol  
Glucocorticoids |
| Idiopathic | Adolescent (10–18 years)  
Middle-aged man |
| Genetic disorders | Osteogenesis imperfecta  
Homocystinuria |
| Chronic illness | Rheumatoid arthritis (juvenile, adult)  
Cirrhosis  
Sarcoidosis  
Renal tubular acidosis |
| Neoplasms | Metastatic cancer  
Bone marrow tumors  
Myeloma  
Lymphoma  
Leukemia  
Mastocytosis |
| Endocrine abnormalities | Pituitary hypersecretion tumor  
Adrenal cortex  
Glucocorticoid excess (hyperplasia, tumor, iatrogenic)  
Ovary  
Estrogen deficiency (postmenopausal, genetic, ovariectomy)  
Testis  
Testosterone deficiency (genetic, castration)  
Parathyroid  
Hyperparathyroidism (primary, secondary)  
Thyroid  
Hyperthyroidism |
| Postmenopausal | Type I osteoporosis |
| Correlated | Type II osteoporosis (male or female) |

**FIGURE 7-44** Specimen radiographs of 2-mm slices through the vertebral body of T2. **A**, The first specimen represents normal bone texture, density, and pattern. **B**, The second specimen shows a moderate degree of osteopenia, with accentuation of the vertical trabeculae and selective loss of the horizontal trabeculae. **C**, The third specimen shows severe osteoporosis, with irregular thin trabeculae and partial central collapse of the superior end plate.
diseases resulting from disturbances in cell linkage

In steroid-induced osteoporosis, osteoclastic activity is high, with relatively normal bone formation (Fig. 7-53). The striking feature of osteoporotic bone on microscopic examination is not only the diminution of trabecular thickness but also the lack of connectivity of the trabeculae with often just sparse islands of short pieces of bone tissue (Fig. 7-54). Many of the trabeculae will be seen to have pointed ends where the bone has been eroded by increased osteoclastic activity (Fig. 7-55).

Until recently, only a bone biopsy could adequately evaluate the activities of osteoclasts and osteoblasts, factors that are critical in the assessment of osteoporosis and the determination of a suitable mode of treatment. However, at present, there are excellent

<table>
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<th>TABLE 7-2 Involutional Osteoporosis</th>
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<td><strong>Epidemiologic Factors</strong></td>
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<td>Age</td>
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<td>Sex (F:M)</td>
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<tr>
<td><strong>Bone Physiology or Metabolism</strong></td>
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<td>Pathogenesis of uncoupling</td>
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<td>Net bone loss</td>
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<td>Rate of bone loss</td>
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<td>Bone density</td>
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<tr>
<td><strong>Clinical Signs</strong></td>
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<td>Fracture sites</td>
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<tr>
<td>Other signs</td>
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<tr>
<td><strong>Laboratory Values</strong></td>
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<td>Serum Ca++</td>
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<tr>
<td>Serum P_i</td>
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<tr>
<td>Alkaline phosphatase</td>
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<td>Urine Ca++</td>
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<td>PTH function</td>
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<td>Renal conversion of 25(OH)D to 1,25(OH)D</td>
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<td>Gastrointestinal calcium absorption</td>
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<td><strong>Prevention and Treatment</strong></td>
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<td>High-risk patients</td>
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Until recently, only a bone biopsy could adequately evaluate the activities of osteoclasts and osteoblasts, factors that are critical in the assessment of osteoporosis and the determination of a suitable mode of treatment. However, at present, there are excellent

Table: Table 7-2 Involutional Osteoporosis

- **Epidemiologic Factors**
  - Age: 55-75 years (Type I) vs. >70 years (F); >80 years (M) (Type II)
  - Sex (F:M): 6:1 vs. 2:1

- **Bone Physiology or Metabolism**
  - Pathogenesis of uncoupling: Increased osteoclast activity; ↑ resorption vs. Decreased osteoblast activity; ↓ formation
  - Net bone loss: Mainly trabecular vs. Cortical and trabecular
  - Rate of bone loss: Rapid/short duration vs. Slow/long duration
  - Bone density: > 2 standard deviations below normal vs. Low normal (adjusted for age and sex)

- **Clinical Signs**
  - Fracture sites: Vertebral (crush), distal forearm, hip (intracapsular) vs. Vertebral (multiple wedge), proximal humerus and tibia, hip (extracapsular)
  - Other signs: Tooth loss vs. Dorsal kyphosis

- **Laboratory Values**
  - Serum Ca++: Normal vs. Normal
  - Serum P_i: Normal vs. Normal
  - Alkaline phosphatase: Normal (↑ with fracture) vs. Normal (↑ with fracture)
  - Urine Ca++: Increased vs. Normal
  - PTH function: Decreased vs. Increased
  - Renal conversion of 25(OH)D to 1,25(OH)D: Secondary decrease due to ↓ parathyroid hormone vs. Primary decrease due to decreased responsiveness of 1-α-H_{25OH}
  - Gastrointestinal calcium absorption: Decreased vs. Decreased

- **Prevention and Treatment**
  - High-risk patients: Estrogen or calcitonin supplementation; calcium supplementation; adequate vitamin D; adequate weight-bearing activity; minimization of associated risk factors vs. Calcium supplementation; adequate vitamin D; adequate weight-bearing activity; minimization of associated risk factors

Note the thin cortices that outline the residual cancellous bone, in which its density is only slightly different from that of the surrounding soft tissues. There is a recent fracture of the femoral neck, which, as is often the case, has drawn attention to the severe osteoporosis in this patient.
biochemical tools for measuring bone breakdown, especially the N-telopeptide level in the urine.

The treatment of osteoporosis should, insofar as possible, be directed toward the underlying etiology. Long-term corticosteroid therapy, excessive alcohol intake, and endocrinopathies such as hyperthyroidism account for a significant number of cases of osteoporosis and should be corrected medically as far as possible. In patients with idiopathic osteoporosis, a number of therapeutic agents have been used with various degrees of success. Exercise is crucial in maintaining skeletal integrity. Calcium supplementation corrects the relative calcium deficiency in the postmenopausal state. At present, most emphasis is placed on the suppression of osteoclastic activity (e.g., by the use of calcitonin and bisphosphonates) and

FIGURE 7-47 Photograph of a sagittal section of a macerated thoracic spine demonstrates the various patterns and degrees of collapse that may be seen within the vertebral bodies. In the upper part of the segment, there is flattening of the vertebral bodies with some anterior wedging. In the lower part, the more typical biconcave compression fractures of the central end plates, which give rise to the so-called ‘fish-mouth’ vertebrae, are visible.

FIGURE 7-48 Photomicrograph taken from a vertebral body in a patient with osteoporosis shows a microfracture of one of the trabeculae. Surrounding the fractured trabecula is a small microcallus. In patients with osteoporosis, such microfractures are abundant in the vertebral bodies (H&E, × 4 obj.).

FIGURE 7-49 A, A radiograph of a sagittal section through a vertebral body in a 19-year-old man. Note the variation in the cancellous bone mass. B, A cross-section through the center of the vertebral body may suggest osteoporosis when compared with the densely packed cancellous bone close to the vertebral end plate (C).
the stimulation of osteoblastic activity (e.g., by the use of oral phosphates or teriparatide parathormone). Although estrogen replacement therapy seems to be theoretically sound, its link with atypical endometrial changes and carcinogenesis has limited its use for the treatment of osteoporosis.

LOCALIZED (TRANSIENT) OSTeofOROSIS

In 1900, Sudeck described a transient yet painful condition of the lower extremity associated with radiographic evidence of localized juxta-articular osteopenia. The disease occurred without obvious cause, although it was possibly related to trauma (Fig. 7-56). This syndrome, usually known as Sudeck’s atrophy, has been related to a reflex sympathetic dystrophy. The symptoms, often involving the entire extremity, include pain, hyperesthesia, and tenderness and are frequently debilitating. The pain varies in severity and character, and is associated with swelling and a decreased range of motion in neighboring joints. The skin may be clammy, cyanotic, and painful to the touch.

In 1959, Curtiss and Kincaid reported a number of cases of a painful localized and transient osteoporosis that involved the hip joints of pregnant women (Fig. 7-57). Since that time, it has become apparent that this may occur without pregnancy and that middle-aged men are also sometimes affected by a similar condition. A migratory form of transient osteoporosis has also been reported, which rather than being restricted to the hip may affect the knee as well as the foot and ankle (Fig. 7-58). This form, which is also associated with swelling of the affected part, has been called regional migratory osteoporosis. In all of these syndromes, the radiographic lesions tend to be juxta-articular.

Laboratory findings are unremarkable. Magnetic resonance imaging (MRI) in these cases of transient osteoporosis reveals evidence of
extensive bone marrow edema. The involved areas show an increased uptake of isotope on technetium bone scanning, and this increased uptake may predate the radiologic evidence of osteopenia by some months. Histopathologic findings have been only infrequently reported; however, microscopic examination of histologic sections has shown thinned-out bone trabeculae with evidence of osteoclastic bone resorption and hypervascularity of the marrow space (Fig. 7-59). In some cases of transient osteoporosis, biopsy has demon-

**FIGURE 7-54** A, Vertebral bone biopsy showing sparse attenuated trabeculae (H&E, × 4 obj.). B, In a higher power view of the same material, the disconnectedness of the trabeculae as well as attenuated appearance can be appreciated (H&E, × 10 obj.).

**FIGURE 7-55** Trabecular perforation by osteoclasts activity results in trabecular disconnects (H&E, × 25 obj.).

**FIGURE 7-56** A and B, Imaging studies of a foot in a patient with reports of severe pain localized to the foot and ankle following trauma. Note the patchy osteopenia and (C) increased isotope uptake, particularly in juxta-articular locations. D, Gross specimen of a section through the foot reveals marked hyperemia in patches, but particularly juxta-articularly. E, Radiograph of a slice of the specimen is shown and demonstrates that the osteopenia corresponds to the hyperemic areas.
Chapter 7

Diseases resulting from disturbances in cell linkage

...evidence of fat necrosis and fibrosis in the marrow, suggestive of an episodic ischemic etiology. If indeed the condition is related to episodic ischemia, then the hyperemia and increased osteoclastic activity that has been observed may be regarded as secondary reparative phenomena. Recent reports have suggested that the condition is due to nondisplaced intraosseous trabecular fractures similar to those seen in insufficiency fractures (see Chapter 11) and this, too, would explain the reported microscopic findings.

Because the lesions usually remit spontaneously within a year or two, the importance of this disorder rests in recognizing its benign nature. It should not be confused with diseases such as osteomyelitis or metastatic cancer, which it may mimic radiologically. Treatment with bisphosphonates or calcitonin have reported to be successful.

IDIOPATHIC OSTEOLYSIS

Primary idiopathic osteolysis is very rare. It is characterized by the spontaneous onset of bone resorption without any obvious cause. Bones that previously appeared normal begin to undergo partial or complete resorption. This process may continue for years, until eventually it ceases spontaneously. The end result is severe deformity and serious functional disability.

FIGURE 7-57 Radiograph of the pelvis of a woman with transient osteoporosis, who had complained for some months of severe pain and weakness in the right hip. Note the osteolysis affecting both sides of the hip joint.

FIGURE 7-58 A. Radiograph of the left knee of a 61-year-old woman who developed severe pain of acute onset in the knee without any obvious local trauma, systemic disease or other antecedent event. The pain was aggravated by weight-bearing and disturbed normal sleep. An area of poorly defined lucency in the distal femur corresponded to increased uptake on a bone scan (B). The differential diagnosis at presentation was tumor or infection. Biopsy revealed a microscopic change in the bone most consistent with transient osteoporosis, and over the following year, the symptoms resolved.

FIGURE 7-59 Photomicrograph of tissue obtained from a patient with transient osteoporosis. There is severe thinning of the bone due to increased osteoclastic resorption and the marrow shows ischemic changes with breakdown of the fat cells (H&E, × 10 obj.).

FIGURE 7-59 Photomicrograph of tissue obtained from a patient with transient osteoporosis. There is severe thinning of the bone due to increased osteoclastic resorption and the marrow shows ischemic changes with breakdown of the fat cells (H&E, × 10 obj.).
Torg and associates have classified the osteolyses into four types: hereditary multicentric osteolysis with dominant transmission, hereditary multicentric osteolysis with recessive transmission, idiopathic nonhereditary multicentric osteolysis with nephropathy, and Gorham’s massive osteolysis.

**Gorham’s Massive Osteolysis**

In 1955, Gorham and Stout reported 24 patients who presented with a monocentric, massive osteolysis. This disease, known as Gorham's osteolysis, disappearing bone disease, or vanishing bone disease, may start at any age and has no familial incidence.

Massive osteolysis is characterized radiographically by localized progressive and extensive reduction in bone density, and morphologically by the replacement of osseous tissue with fibrous tissue and thin-walled dilated vascular channels. Generally detected initially in children or young adults, the disorder usually affects the appendicular skeleton and is often confined to a single bone or to two or more bones centered around a joint. The shoulder and hip are the most common sites of involvement. The clinical course is protracted but...
rarely fatal, with eventual stabilization the most common outcome. Patients may complain of a dull aching pain or the insidious onset of progressive weakness. Radiologic examination reveals initial intramedullary and subcortical ill-defined lucent areas, with a subsequent loss of density extending from one end of the bone to the other. Reactive bone formation is not evident. Characteristic shrinkage or tapering of the long bones may occur (Fig. 7-60). Reported descriptions of whole surgical specimens have featured thin, tapered, soft bone, and in specimens in which the mineralized bone has entirely disappeared, a fibrous band may be seen to replace the original bone. Biopsies of earlier lesions have revealed hypervascular fibrous connective tissue replacing bone; the proliferative vessels may be capillary, sinusoidal, or cavernous (Figs. 7-61 to 7-64).
Ivar Sandstrom (1852–1889). In 1880, Sandstrom published a paper “On a New Gland in Man and Several Mammals—Glandulae Parathyroideae.” He had originally made this discovery while still a medical student. (From the Wellcome Library, London.)

Frederik Daniel von Recklinghausen (1833–1910). In 1891, in a festschrift in honor of the 75th birthday of Rudolf Virchow, von Recklinghausen published the case of a 40-year-old man who had died following a protracted course of fractures, severe bone pain, and wasting disease. At autopsy there were widespread fibrosis, cyst formation, and brown (giant) tumors affecting the skeleton as a whole. In the autopsy notes was the following: “Above the left thyroid gland a lymph gland, red-brown in color is present.” (From the BIUM Collection de Portraits.)

Edward Mellanby (1884–1955). Research conducted by Sir Edward Mellanby led to the discovery that rickets is a disease of malnutrition, curable with regular doses of cod liver oil. Scientist later determined that the condition is a result of vitamin D deficiency. (Photograph by J. Russell & Sons, 1943. From the Wellcome Library, London.)
Calcium and phosphate have crucial roles in many physiologic processes. Intracellular phosphate esters are important in the generation and transfer of cellular energy. Calcium is essential to neuromuscular function, cardiac function, and blood clotting. In addition, calcium is an obligatory coenzyme in many processes and contributes to the continuing integrity of cell membranes. About 85% of the body’s phosphate and 99% of its calcium are contained within the bone as hydroxyapatite.

Calcium homeostasis, which is mainly under the control of the endocrine system, parathyroid hormone (PTH), vitamin D, and calcitonin (CT), depends on the normal functioning of the target organs, that is, the intestines, kidneys, and bone cells. Two principal patterns of bone disease are associated with disturbed calcium homeostasis: osteitis fibrosa cystica (von Recklinghausen’s disease) (Fig. 8-1) and hyperosteoidosis (osteomalacia and rickets) (Fig. 8-2).

**Calcium and Phosphorus Homeostasis**

Optimal neuromuscular function requires precise maintenance of the extracellular calcium ion concentration, even under conditions of dehydration, starvation, or disease. (Most laboratory determinations of blood calcium levels measure total calcium, which includes both ionized calcium, protein-bound calcium, and calcium complexed to other organic ions. However, it is the ionized fraction of calcium that is most important to neuromuscular function.)

Figure 8-3 illustrates calcium and phosphorus homeostasis in a healthy adult with an adequate diet. The calcium and phosphorus are present in three principal pools: the bone tissue, the intracellular fluid, and the extracellular fluid. However, it should be noted that most mineral incorporated into the bone matrix is not available for rapid exchange with the extracellular fluid. Calcium and phosphorus are added to the system through the gut, and lost from the system through the gut, the kidneys, and by sweating. It should be noted that most of the blood calcium and phosphorus removed by glomerular filtration is reabsorbed through the renal tubular epithelium.

The required daily calcium intake is 800 mg of elemental calcium. During adolescence and, for women, during pregnancy and lactation, this amount needs to be increased to 1200 mg per day. Normally most calcium is obtained from dairy products, and since 1 cup of milk is equal to 300 mg of calcium, it requires 3 to 4 cups of milk or the equivalent cheese or yogurt per day. Needless to say, many people have a diet that is deficient in calcium.

Figure 8-4 illustrates the endocrine control of calcium and phosphorus homeostasis. Parathyroid gland activity is largely regulated by the level of Ca++ in the extracellular fluid; an increase in serum Ca++ suppresses PTH production, and vice versa. Once in the circulation, biologically active PTH has a short half-life, probably on the order of less than 5 minutes. It is degraded by enzymatic cleavage, mainly in the liver but also in the kidney and in the parathyroid gland itself. (Therefore, laboratory assays for measurement of PTH are primarily of biologically inactive fragments.)

PTH regulates the conversion of 25-hydroxy vitamin D (25-OH-D) in the kidney to its active form, 1,25-dihydroxyvitamin D (1,25(OH)2-D). Additionally PTH acts on the renal tubules to increase the tubular reabsorption of calcium while decreasing the reabsorption of phosphorus. PTH directly stimulates the osteoblasts to synthesize new bone and, through upregulation of RANK-L gene relatively late in the process of osteoblast differentiation, stimulates osteoclastic resorption of bone and, hence, the release of Ca++ into
the extracellular fluid. RANK-L, essential to osteoclastogenesis, has a decoy receptor osteoprotegerin (OPG), which negatively regulates the process; because PTH has an inhibitory effect on OPG, changes in both RANK-L and OPG levels following PTH exposure result in increased potential for osteoclastogenesis.

Figure 8-5 shows the pathway for vitamin D hormone. The principal natural source of vitamin D is the conversion of 7-dihydrocholesterol in the skin, through the action of ultraviolet irradiation, to vitamin D$_3$, which can then be stored in fat and muscle cells. (Vitamin D$_2$, commercially produced by ultraviolet irradiation of plant sterols, is biologically equipotent to D$_3$; in the United States, it is added extensively to milk, certain other foods, and vitamin supplements. Vitamins D$_2$ and D$_3$ circulate together in the body, are biologically interchangeable, and are usually referred to in the aggregate as vitamin D.)

It is believed that exposure to sunlight of no more than 10 to 15 minutes can provide the body with the amount of vitamin D required for the next 3 days. Only a small part of the skin needs to be exposed for adequate production of vitamin D. However, there is evidence that the chronic use of sunscreens, especially by the elderly, may occasionally cause frank vitamin D deficiency, and it is recommended that supplemental vitamin D is required.

Vitamin D is itself inactive, and conversion to 25-OH-D takes place in the liver. The hepatic conversion of vitamin D to 25-OH-D can be disturbed by liver disease or by administration of anticonvulsant drugs, such as phenytoin. Although 25-OH-D has only minimal physiologic activity, nevertheless in pharmacologic dosage, it can promote both gut absorption of calcium and bone mineralization.

There is a pathway for enterohepatic recirculation of 25-OH-D and its metabolites that are excreted into the bile. For this reason, intestinal malabsorption or anatomic loss of intestinal absorptive area can interfere with the reabsorption of these substances and inexorably deplete the systemic pool of vitamin D. In this way, severe vitamin D deficiency can develop, even though exposure to sun and to dietary sources of vitamin D is adequate.

In the kidney, through the action of specific alpha-hydroxylases, 25-OH-D is converted to either 24,25(OH)$_2$D or 1,25(OH)$_2$D. Therefore, patients with advanced renal disease become deficient in both of these forms of the active vitamin, which is probably the primary reason for the frequency and severity of bone disease associated with kidney failure.

The action of 24,25(OH)$_2$D on bone metabolism is being actively investigated. Although it only weakly accelerates the absorption of calcium by the gut, it is believed to have an important role in osteoblast cell differentiation. By contrast, 1,25(OH)$_2$D is the most biologically potent form of vitamin D known and has multiple and profound actions on osseous metabolism. It accelerates the gut absorption of calcium, promotes bone mineralization, and inhibits bone resorption.
absorption of calcium and phosphorus, promotes bone cell differentiation and the mineralization of osteoid, and enhances the sensitivity of bone to PTH-induced osteoclastic or osteocytic resorption to maintain serum calcium. Perhaps most importantly for patients on maintenance renal dialysis, it directly suppresses overactive parathyroid cells and enhances parathyroid suppression by ambient calcium levels.

In addition to its effects on bone metabolism, 1,25(OH)\(_2\)D also has other biologic actions, including inhibition of the production of interleukin-2 and immunoglobulins, and the stimulation of insulin and thyroid-stimulating hormone secretion. With respect to its effect on cell proliferation and differentiation, it is of interest that 1,25(OH)\(_2\)D induces monocytes to become multinucleated giant cells, which act in vitro as osteoclast-like cells.

The physiologic role of human CT is not completely understood, but current theories are focused on the possibility that it is more important as a regulator of skeletal homeostasis rather than calcium homeostasis. In pharmacologic doses, CT inhibits osteoclastic resorption of bone, suggesting that it might act in vivo to conserve skeletal mass. In this regard, it has been reported that women have lower whole plasma immunoreactive CT (iCT) concentrations than men, and that peak calcium-stimulated iCT concentrations decline with age. Although the data are controversial, some investigators have suggested that CT secretion decreases at the time of menopause and can be stimulated by estrogen replacement. It is possible, therefore, that a relative, progressive deficiency of CT in postmenopausal women is a contributing cause of age- and sex-related bone loss.

**Hypercalcemia**

Hypercalcemia is relatively common, and its causes are numerous (Box 8-1); symptoms of hypercalcemia may arise in any organ system (Box 8-2). Mild hypercalcemia is common in patients with widespread lytic bone metastases and with multiple myeloma, and on occasion, it may be seen in cases of sarcoidosis or vitamin D intoxication. However, the most important cause of significant hypercalcemia is hyperparathyroidism.

**HYPERPARATHYROIDISM (OSTEITIS FIBROSA CYSTICA; VON RECKLINGHAUSEN’S BONE DISEASE)**

Overproduction of parathyroid hormone occurs as either a primary or a secondary condition. Primary hyperparathyroidism (HPT) normally results from an adenoma, rarely from primary hyperplasia (etiology unknown) or carcinoma (Figs. 8-6 and 8-7).
Blood chemistries usually reveal marked hypercalcemia, and usually hypophosphatemia. Patients with this disorder are in general between the third and fifth decades of life. Although many patients are asymptomatic, the most common clinical presentation of primary hyperparathyroidism is renal colic secondary to stone formation; bone pain may be present in a small percentage of patients. As hypercalcemia becomes more pronounced, nausea, vomiting, weakness, and headaches may appear. On rare occasions, a patient presents with a hypercalcemic crisis, leading to shock, kidney failure, and death. Mild hyperparathyroidism in elderly individuals presents clinically as osteoporosis. Surgical removal of the neoplastic gland or of some of the hyperplastic glands is the treatment of choice.

Secondary hyperparathyroidism is the result of chronic renal failure, its inevitable consequence is further derangement of mineral and bone metabolism. This is present even in patients with mild reductions of glomerular filtration rate; and becomes progressively more severe as renal function declines further.

Secondary hyperparathyroidism in renal failure results from
1. A fall in ionized calcium concentration as a consequence of phosphate retention
2. Malabsorption of calcium through the gut

Furthermore, in addition to the loss of 1-alpha hydroxylating capacity as renal cell mass declines, there is also an inhibition of 1,25(OH)₂D production by increased phosphate. Because 1,25(OH)₂D directly suppresses the parathyroid cells, loss of renal production of 1,25(OH)₂D encourages secondary hyperparathyroidism to develop more rapidly and severely.

When PTH levels rise sufficiently, severe bone resorption gives rise to significant hypercalcemia, bone pain, and fractures. The combined effects of hypercalcemia and hyperphosphatemia lead to extensive metastatic calcification in blood vessels and at other sites. At this stage, subtotal parathyroidectomy may be necessary.

In patients with chronic renal disease, dietary phosphate restriction can reverse the above-mentioned sequence of events to a certain extent.
Section iii

Metabolic Disturbances

In children with stable chronic renal failure, phosphate-restricted diets have been shown to increase 1,25(OH)2D concentrations and decrease PTH levels, thereby partially reversing the hormone imbalance.

Medical treatment of secondary HPT in dialysis patients consists of phosphate restriction, administration of phosphate binders, the use of a high-calcium dialysate, and oral or intravenous supplementation with 1,25(OH)2D. When adequate, such therapy usually obviates the necessity for subtotal parathyroidectomy (which if it has to be done, may be followed by significant postoperative hypoparathyroidism). Therapeutic control of the hyperparathyroidism, whether surgical or medical, is followed by a dramatic regression of the histologic changes in the bone and subsequent improvement of the radiologic abnormalities. The serum alkaline phosphatase normalizes, and PTH may fall to levels seen in dialysis patients who do not have HPT.

In the past, a minority of patients with chronic renal failure had accumulation of aluminum (derived from aluminum-contaminated dialysate or aluminum-containing phosphate binders by mouth) at the mineralization front that blocked calcification, resulting in osteomalacia with further disturbance of the skeletal function (Fig. 8-8).

Morphologic Findings

In both primary and secondary hyperparathyroidism, the radiologic and pathologic features are similar. Radiologic examination may reveal diffuse osteopenia or circumscribed lucent areas. However, the most characteristic changes include erosion of the tufts of the phalanges and subperiosteal cortical resorption, especially visible on the radial side of the middle phalanges (Fig. 8-9). Other sites at which erosive resorption may be seen are the symphysis pubis (Fig. 8-10), the distal clavicles (Fig. 8-11), and the end plates of the vertebral bodies (Fig. 8-12), as well as the lamina dura (i.e., the layer of the dense bone at the roots of the teeth) (Fig. 8-13). The skull may show a granular demineralization, the so-called ‘salt and pepper’ appearance (Figs. 8-14 and 8-15).

Microscopic examination of bone biopsies in patients with hyperparathyroidism demonstrate an increased number of osteoclasts on the bone surfaces (even on periosteal surfaces), and a characteristic ‘tunneling’ or ‘dissecting’ resorption of trabeculae (Figs. 8-16 to 8-18; see also Fig. 8-1). Other findings include intraosseous resorption of pericellular bone by osteocytes (osteocytic osteolysis), increased amounts of

<table>
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<tr>
<th>BOX 8-1 Differential Diagnosis of Hypercalcemia</th>
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<tr>
<td>Primary hyperparathyroidism</td>
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<tr>
<td>Immobilization (especially with associated conditions, e.g., generalized Paget’s)</td>
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<tr>
<td>Malignant disease</td>
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<td>Multiple myeloma, breast carcinoma</td>
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<tr>
<td>Humoral peptide of malignancy (carcinoma of lung, esophagus, head, and neck, renal cell, ovary, bladder)</td>
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<tr>
<td>Ectopic production of 1,25-dihydroxyvitamin D (lymphoma)</td>
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<tr>
<td>Thyrotoxicosis</td>
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<tr>
<td>Sarcoidosis and other granulomatous disease</td>
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<tr>
<td>Drug induced</td>
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<tr>
<td>Vitamin D</td>
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<tr>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Tamoxifen</td>
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<tr>
<td>Acute and chronic renal failure</td>
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<td>Total parenteral nutrition</td>
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<td>Familial hypercalcemic hypercalcemia</td>
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<table>
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<tr>
<th>BOX 8-2 Clinical Features of Hypercalcemia</th>
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<tr>
<td>1. Neuromuscular</td>
</tr>
<tr>
<td>a. Headache</td>
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<tr>
<td>b. Muscle weakness</td>
</tr>
<tr>
<td>c. Altered states of consciousness (confusion, lethargy, stupor, coma)</td>
</tr>
<tr>
<td>d. Hyporeflexia</td>
</tr>
<tr>
<td>2. Gastrointestinal</td>
</tr>
<tr>
<td>a. Anorexia</td>
</tr>
<tr>
<td>b. Nausea</td>
</tr>
<tr>
<td>c. Vomiting</td>
</tr>
<tr>
<td>3. Renal</td>
</tr>
<tr>
<td>a. Nephrolithiasis</td>
</tr>
<tr>
<td>b. Polyuria</td>
</tr>
<tr>
<td>c. Polydipsia</td>
</tr>
<tr>
<td>4. Others</td>
</tr>
<tr>
<td>a. Bradycardia</td>
</tr>
<tr>
<td>b. Metastatic calcification</td>
</tr>
<tr>
<td>c. Dehydration</td>
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FIGURE 8-6 A, Posterior aspect of the pharynx, and commencement of the esophagus and trachea. Note the usual position of the parathyroid glands. Normally measuring no more than 4 to 5mm, they may be difficult to locate, especially when they are displaced. B, Photomicrograph of normal parathyroid gland shows glandular tissue admixed with fat (H&E, x 2.5 obj.).
**FIGURE 8-7**
A. Parathyroid adenoma: large tan nodule measuring approximately 2 cm on the left side of the lower pole of the thyroid. B. Photomicrograph of parathyroid adenoma shown in A. The cells are of one type, chief cells, arranged in small acini and cords. Characteristically, no fat is visible in the adenomatous tissue (H&E, × 10 obj.).

**FIGURE 8-8** Photomicrograph of a section of bone with increased osteoid stained with aurin tricarboxylic acid stain, which stains aluminum bright red. The red stain is concentrated at the mineralization front; it has been proposed that the presence of aluminum at this site blocks further mineralization of the bone (Nomarski optics, × 10 obj.).
FIGURE 8-9. A. Clinical radiograph of the hand shows resorption of the tufts of the terminal phalanges. The characteristic subperiosteal resorption of the middle and proximal phalanges, more marked on the radial side of the phalanges, is also present. B. In this close-up radiograph of the middle and ring finger of the left hand, the erosion of the medial cortical bone on the proximal and middle phalanges is clearly seen. Note, too, the calcification of the digital arteries in this patient with severe secondary hyperparathyroidism. (A courtesy of Dr. Alex Norman; B courtesy of Dr. Edward McCarthy.)

FIGURE 8-10. A. Gross appearance of a symphysis pubis obtained at autopsy from a patient with hyperparathyroidism shows hyperemia, fibrosis, and resorption of the bone on each side of the symphysis. B. Radiograph of the specimen.

FIGURE 8-11. A characteristic anatomic site in which to observe erosion in hyperparathyroidism is the distal clavicle. In this specimen radiograph, resorption is clearly seen, with loss of the smooth cortex and replacement by a lacy irregular outline.

FIGURE 8-12. Specimen radiograph of a slice taken through a vertebra in a young person with hyperparathyroidism shows the irregularity and resorption of the cortical bone, particularly the end plates of the vertebral bodies.

FIGURE 8-13. Radiograph of the lower second molar tooth in a patient with primary hyperparathyroidism shows loss of the dense lamina dura normally present around the tooth socket.
Chapter 8  Bone Disease Resulting from Disturbances in Mineral Homeostasis

Figure 8-14  Hyperparathyroidism: clinical radiograph of a skull showing 'salt and pepper' appearance. Note the irregularity of the outer cortex posteriorly.

Figure 8-15  Radiograph showing patchy blastic reparative changes after parathyroidectomy. This appearance could be mistaken for Paget's or metastatic disease. (Courtesy of Dr. Alex Norman.)

Figure 8-16  Photomicrograph to show severe osteoclastic bone resorption in a patient with primary hyperparathyroidism. Note the mild periosteal fibrosis associated with bone formation on the inferior bone surface (H&E, ×25 obj.).

Figure 8-17  A specimen radiograph of a slice of vertebral body affected with primary hyperparathyroidism. The architecture of the cancellous bone is disturbed and the trabeculae contain lytic lines within them, due to the dissecting resorption characteristic of this condition. Note the partial resorption of the end plates.

Figure 8-18  A scanning electron micrograph of cancellous bone demonstrates numerous irregular erosions on the bone surface, due to osteoclastic resorption (×750 magnification).
Section III
Metabolic Disturbances

woven bone production, and marrow fibrosis, especially abutting trabecular surfaces (Fig. 8-19). (The finding of peritrabecular fibrosis should be distinguished microscopically from the more generalized fibrosis seen in association with myelofibrosis, which generally starts within the marrow and away from the bone surfaces [see Chapter 9].)

Occasionally, patients who have undiagnosed hyperparathyroidism present on radiologic examination with one or more lytic lesions, which may suggest a neoplasia. These lesions, particularly evident in the diaphysis of long bones, the jaw, or the skull, are the so-called brown tumor of hyperparathyroidism, which on microscopic examination, are composed of many clustered giant cells in a fibrovascular cellular stroma (Figs. 8-20 and 8-21). The brown tumor of hyperparathyroidism must be differentiated histologically from a giant cell tumor, as well as giant cell reparative granuloma and aneurysmal bone cyst, to which it is very similar (see Chapter 19).

In many patients with chronic renal failure, increased density of the axial skeleton can be seen on radiographic examination: the so-called rugger jersey spine. Histologically, this increased density appears as increased woven or immature bone superimposed on the usual characteristics of hyperparathyroidism (Fig. 8-22). Both the radiologic and histologic changes may occasionally be confused with those of Paget’s disease.

Hypercalcemia not Associated with Hyperparathyroidism (Pseudohyperparathyroidism)

Hypercalcemia may occur in association with certain rare tumors that secrete parathyroid hormone–like substances referred to as parathyroid hormone–related protein (PTHrP). The tumors most commonly associated with this type of humoral hypercalcemia are squamous cell lung cancer, other squamous cell tumors, renal cell,
and urogenital tract carcinoma. When a small occult tumor is the cause of the hypercalcemia and hyperparathyroid-like condition, the correct diagnosis may be delayed for some time. In these cases of humoral hypercalcemia of malignancy, the radiologic and microscopic appearance of skeletal tissue cannot be distinguished from that associated with primary hyperparathyroidism. The most important clue that the hypercalcemia is arising from a malignancy in patients with this rare condition of pseudohyperparathyroidism is that PTHrP is usually not detected by conventional assays for PTH, and consequently the measurable PTH levels are paradoxically profoundly depressed.
Although uncommon, the effects of vitamin A (retinoic acid) intoxication are occasionally seen in food faddists. Irritability, lethargy, vomiting, loss of appetite, scaly skin, and hair loss are the usual presenting symptoms. Severe hypercalcemia may result from increased osteoclastic activity and bone resorption leading to osteoporosis and fractures. Vitamin A has a role in the proliferation and differentiation of several tissues, and in infants and young children, hypervitaminosis A may result in accelerated maturation of the growth plates with central physeal arrest, resulting in a slow down of bone growth activity (Fig. 8-23).

**Hypocalcemia**

With hypocalcemia, the most common symptom is neuromuscular irritability (Box 8-3), however, the condition may be asymptomatic. Like hypercalcemia the causes of hypocalcemia are numerous. The most common cause is vitamin D deficiency. Less common are hypophosphatemia (vitamin D–resistant rickets), hypothyroidism, and hypomagnesemia (Box 8-4). Rarely, it is life-threatening.

### HYPEROSTEOIDOSIS

Hyperosteoideosis is a histologic term that describes an increase in the relative proportion of unmineralized to mineralized bone tissue. There are three basic causes of hyperosteoideosis.

1. A marked increase in the rate of bone formation, so that a prominent band of osteoid is present on the bone surface (Fig. 8-24). In this case, labeling with tetracycline reveals a thick, granular, and dense mineralization front.

2. Interference with calcium deposition at the mineralization front as happens in aluminum toxicity and, to a lesser extent, with iron overload. In this case, a wide osteoid seam is observed, usually with flat, inactive osteoblasts at the surface (Fig. 8-25). The mineralization front is sharply demarcated and often at a reversal line. Tetracycline labeling fails to show any uptake at the mineralization front.

3. Most important, a lack of available calcium salts for mineralization of the bone; the clinical terms used to describe this are rickets and osteomalacia. Rickets is a disorder of mineralization of the bone matrix in children; it involves both the growth plate (epiphysis) and newly formed trabecular and cortical bone. Osteomalacia, a defect in bone matrix mineralization in adults, is now the more common form of the disease.
Osteomalacia has a number of etiologies (Box 8-5). The availability of vitamin D may be decreased by poor nutritional intake, lack of sunlight, or by renal or hepatic disease. Calcium availability may also be disturbed by lack of calcium in the diet or by a malabsorption syndrome. Congenital defects in the renal tubules, leading to deficient reabsorption of phosphate and calcium into the blood, also result in rickets and osteomalacia (hypophosphatemic rickets; see later).

The most common symptom of osteomalacia in adults is bone pain, sometimes localized, more often bilateral and symmetrical; often initially mild but gradually becoming severe. There may also be proximal muscle weakness, which is often profound. The serum calcium tends to be low normal, the phosphate very low, and the alkaline phosphatase very high (released from stimulated osteoblast). Serum 25-OH-D levels are usually markedly depressed, whereas 1,25(OH)2D levels may be initially normal, although they, too, eventually fall. PTH levels tend to rise considerably, resulting in relative preservation of the serum calcium.

Radiologic examination may reveal generalized osteopenia as a result of the loss of calcified matrix. Classically, multiple bilateral and symmetrical cortical lucent areas in the ribs, scapula, pelvis, and femoral neck are present. These lucent areas represent stress fractures and typically lie perpendicular to the long axis of the bone; they are sometimes referred to as Looser’s zones or Milkman’s lines (Fig. 8-26). A radioisotope scan is the most helpful examination used to identify these fractures (Fig. 8-27). In general, the axial skeleton, with its higher rate of turnover (e.g., the vertebrae, pelvis, ribs, and sternum), is more often affected clinically than the peripheral skeleton.

Microscopic examination of undecalcified diseased bone reveals a marked increase in the amount of nonmineralized matrix (osteoid) on the surfaces of the bone trabeculae and lining the haversian canals of the cortical bone (Fig. 8-28). Determination of the severity of osteomalacia requires quantitative histomorphometry, and this reveals that at least 10% and usually much more of the bone mass consists of nonmineralized bone matrix. Tetracycline uptake studies show patchy, blurred uptake at the mineralization fronts (Fig. 8-29). Resorptive changes typical of secondary hyperparathyroidism are also present in many cases. Microscopic examination of the stress fractures reveals poorly mineralized callus and fibrous tissue.

Rickets

In the early 19th century, as a result of the industrial revolution, the large northern European cities became increasingly crowded and polluted. Because of poor diet and little exposure to sun, the children commonly developed severe and debilitating rickets, which among the
poor was almost universal. (Nowadays classic rickets, resulting from a deficiency of vitamin D, is only rarely seen, and in the United States, the most common cause of rickets is renal tubular dysfunction.)

Morphologically, rickets is characterized by widespread skeletal deformities principally affecting the foci of most rapid growth. The disease may be recognized in patients as young as 6 months of age, at which time thinning and softening of the calvaria and bulging fontanelles may be evident. These cranial changes usually diminish by 2 years of age but are followed by other dramatic skeletal changes, including beading of the costochondral junctions of the ribs (the so-called rachitic rosary) (Fig. 8-30), a depression along the line of the rib-diaphragm attachment (Harrison’s groove), and a chicken-breasted appearance. In particular, the wrists, knees, and ankles may be enlarged due to failure of the metaphyseal primary spongiosa to mineralize (Fig. 8-31). Eventually curvature of the long bones develops, especially anterior curvature of the tibia. Spinal abnormalities, including dorsal kyphosis, scoliosis, and lumbar lordosis may diminish height.

Radiologic examination reveals a widened and irregular growth plate, with a cup-shaped concavity and flaring of the metaphyseal end of the bone (Fig. 8-32). These changes correlate microscopically with the presence of irregular, disorderly columns of proliferating cartilage in the growth plate and tongues of proliferating irregular cartilage extending into the adjacent bone (Fig. 8-33). These findings are associated with absence of the calcified zone of the cartilage and a poorly formed primary spongiosa. The most striking histologic change is the presence of large amounts of nonmineralized bone throughout the skeleton. Stress fractures, similar to those seen in osteomalacia, are often present.

**HYPOPARATHYROIDISM**

Most commonly, hypoparathyroidism follows extensive neck surgery, especially total thyroidectomy with accidental parathyroidectomy. Very rarely, it is due to hypoplasia of the parathyroid glands. Treatment is aimed at restoration of serum calcium to a low normal level. Elemental calcium and vitamin D are the usual therapeutic agents used.

Pseudohypoparathyroidism refers to the rare genetic condition, characterized by increased levels of circulating parathyroid hormone associated with glandular hyperplasia, which is paradoxically associated with hypocalcemia and hyperphosphatemia. This biochemical hypoparathyroidism results from resistance of the bone and kidneys (i.e., the target organs) to the biologic actions of PTH, even in the face of elevated levels of PTH. This disorder is inherited as an autosomal dominant trait, but mutations have not been found in the PTH gene or PTH receptor gene. It is currently believed that there is a molecular defect in the GNAS1 gene. In very rare cases, patients with this condition demonstrate resistance to multiple hormones and demonstrate short stature, subcutaneous ossification, and mental retardation, a condition known as Albright’s hereditary osteodystrophy.

**HYPOPHOSPHATEMIA**

Hypophosphatemia may result from any number of causes, most of which are acquired, but there are some hereditary causes.
Among the more common causes are increased urinary phosphate loss caused by lowering of the renal tubule threshold for phosphate reabsorption (as seen in primary hyperparathyroidism) and therapeutic administration of diuretic agents. The condition may also be traced to decreased intestinal absorption, as seen in vitamin D deficiency, and malabsorption syndromes; other causes include starvation and the excessive use of phosphate-binding antacids. Acute hypophosphatemia also occurs after uptake of phosphorus from the serum into the cells, as seen after insulin administration, and in states of respiratory alkalosis, as in salicylate poisoning, sepsis, and fever. Severe hypophosphatemia may cause cell damage with potentially serious clinical consequences; examples include erythrocyte hemolysis, leukocyte and platelet disorders, defects of the peripheral and central nervous system, myopathy, and rhabdomyolysis.

In bone, the main consequence of hypophosphatemia is osteomalacia. This impaired mineralization appears to be a purely extracellular problem arising from changes in the calcium and

**FIGURE 8-30**

A. Rickets: dissected specimen of the rib cage shows prominence of the costochondral junctions because of swelling. This gives rise to the so-called rachitic rosary. B. Radiograph of a portion of this specimen demonstrates that the swelling results from irregularity and poor mineralization of the metaphysis with a characteristic ‘cupping’ at the junction of the cartilage and bone. C. Photomicrograph of the costochondral junction in a patient with rickets shows widening of the growth cartilage region with irregularity at the cartilage-bone interface and poorly mineralized, disorganized primary spongiosa (H&E, × 4 obj.).
phosphate concentration product (Ca × P), which reflects the extent of saturation of extracellular fluid with respect to these ions. Laboratory studies in most patients with acquired hypophosphatemia reveal normal glomerular filtration rates, normal to high levels of serum calcium, a markedly lowered level of serum phosphorus, and elevated levels of alkaline phosphatase. PTH levels may be suppressed. 1,25(OH)₂D levels should be elevated but frequently are not, and may even be low. Bone biopsy specimens reveal characteristics of osteomalacia indistinguishable from those caused by vitamin D deficiency.

Most hypophosphatemic states can be corrected medically and do not progress to development of severe skeletal aberrations. However, uncorrected hypophosphatemia may lead to severe skeletal sequelae, especially in growing children.

Osteomalacia due to acquired hypophosphatemia is sometimes seen in association with a variety of benign mesenchymal tumors, particularly benign fibrovascular tumors, which are often found in the sinuses, sometimes in the skin or bone, and may be extremely difficult to locate (rarely it may occur in metastatic prostate cancer). The tumors responsible for oncogenic osteomalacia are often characterized by distinctive “grungy” matrix calcification and production of FGF-23, which impairs phosphate reabsorption by renal tubules (Fig. 8-34). A marked reduction in serum 1,25(OH)₂D is usually
observed, however 25(OH), vitamin D levels are normal. Complete excision of the tumor usually leads to resolution of the biochemical abnormalities and the osteomalacia. A recurrence of the tumor is usually made apparent by a reappearance of osteomalacia.

**Familial Hypophosphatemia (Familial X-Linked Hypophosphatemic Rickets; Vitamin D–Resistant Rickets; Refractory Rickets)**

Familial hypophosphatemic rickets is a genetic disease that is transmitted as an X-linked dominant trait and is usually manifested by the second year of life. The disease is thought to be caused by mutation in the gene encoding FGF-23 (the humoral factor implicated in oncogenic osteomalacia). Typically, the patient’s urinary excretion of phosphorus is increased. The disorder is clinically characterized by childhood rickets with associated growth retardation and poor dental development (Fig. 8-35). The condition is unresponsive to physiological doses of vitamin D.

In middle age, other clinical problems begin to appear, with mineralization of the spiral ligaments and thickening of the neural arches. There is loss of mobility of the spine, shoulders, elbows, and hips. Reduction in the diameter of the spinal canal may lead to cord compression at more than one level.

The primary biochemical defect for this disorder of mineral metabolism remains unknown, although the site of the renal phosphate transport defect has been localized to the brush border membrane of the proximal convoluted tubule.

X-linked hypophosphatemic rickets (caused by mutation in the phosphate-regulating endopeptidase gene, **PHEX**), has long been recognized as being different from any other form of rickets and osteomalacia in its clinical manifestations, pathogenesis, and difficulty of treatment. The disease is regarded primarily as a genetic defect of renal tubule phosphate transport, and this concept has led to treatment with phosphate supplements and large doses of vitamin D. However, successful therapy, particularly full healing of the mineralization defects, usually requires that the phosphate therapy be combined with supraphysiologic dosages of 1,25(OH)$_2$D.

**FANCONI’S SYNDROME (RENAL GLYCOUSURIC RICKETS)**

Fanconi’s syndrome may be genetic or acquired later in life. Common causes of Fanconi’s syndrome in children are genetic defects impairing the body’s ability to break down certain compounds, such as the amino acid cysteine (cystinosis), fructose (fructose intolerance), galactose (galactosemia), and glycogen (glycogen storage diseases). Cystinosis is the most common cause of Fanconi’s syndrome in children.

In adults, Fanconi’s syndrome can be caused by various acquired disorders that damage the tubules of the kidneys. This damage can be caused by exposure to heavy metals such as lead, mercury, and cadmium. Patients with these disorders exhibit normal glomerular function, a decreased level of serum carbon dioxide, normal to low levels of serum calcium, low levels of serum phosphorus, and elevated levels of alkaline phosphatase.

Radiographic examination may reveal diffuse osteopenia and stress fractures. Irregular and widened epiphyseal cartilage zones are clearly seen in children, but the dramatic increase in nonmineralized bone observed in patients with rickets is not apparent. In patients with Fanconi’s syndrome associated with cystinosis, cystine deposits are present in the bone and in the visceral organs.

The osteomalacia is believed to result principally from the severe hypophosphatemia caused by renal tubule dysfunction. Amino acid deficiency may contribute to growth retardation.

**HYPOMAGNESEMIA**

Magnesium is the second most abundant cation in the intracellular fluids and essential to neurochemical transmissions and many enzyme activities. Magnesium deficiency is common and may be present in as many as 10% of patients admitted to general hospitals and more than half the patients in medical intensive care units. Hypocalcemia is commonly associated with chronic magnesium deficiency and under these circumstances is best treated by magnesium replacement. The hypocalcemia appears to be related to impaired PTH secretion in patients with chronic magnesium deficiency and, in general, patients with hypocalcemia of this type usually have normal or low normal PTH levels.

**Soft Tissue Calcification**

**METASTATIC CALCIFICATION**

Metastatic calcification is caused by an increased calcium phosphate product in the blood, and may result from hypercalcemia or hyperphosphatemia, or both. It is commonly associated with hyperparathyroidism, sarcoidosis, metastatic disease, and myeloma (Fig. 8-36). Metastatic calcification is amplified in patients with hypermetabolic states who have undergone prolonged periods of bed rest.

The calcification may be both intracellular and extracellular. Mineral deposition is particularly likely to occur in the kidneys (Fig. 8-37), alveolar walls of the lungs, cornea, conjunctiva, and gastric mucosa (i.e., those areas subject to the large pH changes), as well as in the media and intima of the peripheral arteries.

**TUMORAL CALCINOSIS**

Tumoral calcinosis is a rare inherited condition that primarily, but not exclusively, affects black people in otherwise good health. The responsible genes are **FGF23, GALNT3, and KL**. The disease usually presents in the second decade of life and is characterized by deposition of painless calcific masses around the hips, elbows, shoulders, and gluteal areas (i.e., areas subject to movement and/or pressure) (Figs. 8-38 and 8-39). A familial incidence has been reported. In rare instances, intra-articular or intraosseous deposits may also occur (Figs. 8-40 and 8-41).
FIGURE 8-36 Posteroanterior view of the distal forearms and hands of a 48-year-old woman treated by long-term dialysis for chronic renal failure with resultant secondary hyperparathyroidism. There is soft tissue and vascular calcification, characteristic findings in this condition. An arteriovenous fistula from hemodialysis has occluded and calcified, and is clearly seen in the soft tissue adjacent to the radial metaphysis (left).

FIGURE 8-37 Photomicrograph of the kidney in a patient with prolonged hypercalcemia resulting from a parathyroid adenoma. Extensive calcium deposits are seen in relation to the proximal tubules (H&E, × 4 obj.).

FIGURE 8-38 A, Photograph of a young black woman with extensive subcutaneous calcium deposits (tumoral calcinosis) around the elbows and along the extensor surfaces of the forearm. B, Radiograph of this patient’s arm shows the extent of the calcified mass. C, Cut surfaces of the excised specimen. D, Photomicrograph of a calcium apatite deposit in tumoral calcinosis. Note the histiocytic and giant cell response at the edge of the calcified deposit, which is seen here as a dark blue-purple area to the right of the picture (H&E, × 10 obj.).
The lesions may be massive, are often bilateral, and they affect multiple sites. The patient’s serum phosphate level is usually elevated. Although the hyperphosphatemia should suppress 1,25(OH)2D production, the serum levels tend to stay paradoxically normal. Surgical excision is the most successful form of treatment, although recurrences are common. Medical treatment to control the hyperphosphatemia (e.g., a low phosphate diet and oral administration of phosphate binders) is an important adjunct to surgical excision. (We have seen an instance of correction of hyperphosphatemia and radiologically documented disappearance of a large tumor mass achieved by the use of phosphaturic diuretics.)

Microscopic examination of tissues from these patients reveals calcific deposits that are surrounded by a mild infiltration of both histiocytes and chronic inflammatory cells. Some multinucleated giant cells may be present. X-ray diffraction studies have shown that the deposits are mainly formed of hydroxyapatite crystals.

**CALCIFICATION IN INJURED TISSUE**

Deposition of calcium hydroxyapatite in soft tissues may also occur as a complication of trauma and scleroderma. Dead tissue that does not

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**FIGURE 8-38—CONT’D** E. Occasionally as seen in this photomicrograph, because of variations in processing, the calcium apatite deposits appear pink rather than blue, and in such a case, their true nature may not be apparent to the examining histopathologist (H&E, × 10 obj.).

**FIGURE 8-39** A, Radiograph of a 56-year-old woman with tumoral calcinosis who presented with a mass in the buttock. B, Computed tomography scan of the mass. C, Photograph of the excised mass, which is well encapsulated. D, Photograph of the cross-section.
Section III: Metabolic Disturbances

undergo rapid absorption frequently becomes calcified. This type of calcification, which is not related to any disturbance in calcium homeostasis, is called dystrophic calcification. Calcification is common in areas of coagulation necrosis (e.g., in cases of infarction), in caseous necrosis seen in patients with tuberculosis, and in areas of fat necrosis (Fig. 8-42). Of particular interest to orthopaedic surgeons is the calcification that is common in tendons, ligaments, and bursae (Figs. 8-43 to 8-45). A common clinical presentation for patients with dystrophic calcification is the presence of a calcified mass in the lateral compartment of the knee (Fig. 8-39). Clinical presentation for patients with dystrophic calcification is typically characterized by the presence of a calcified mass in the lateral compartment of the knee (Fig. 8-39).
**Figure 8-43** A. Radiograph of an anteroposterior view of the shoulder demonstrating calcific tendinitis. B. A low-power photomicrograph showing necrotic tissue with focal deposits of hydroxyapatite in the upper part of the image and mixed inflammatory tissue in the lower (H&E, × 4 obj). C. A higher power reveals many giant cells, histiocytes, and scattered lymphocytes with small and large foci of calcium deposition (H&E, × 25 obj).

**Figure 8-44** A. Radiograph of the upper femur of a 58-year-old man who presented with a 1-year history of sharp, intermittent pain in the right thigh. The bone scan was hot. B. Computed tomography scan shows bone erosion, which was misinterpreted as evidence of malignancy, and the upper femur was resected without a biopsy being performed. C. Photograph showing calcification occurring in the region of the linea aspera. Microscopically, the findings were similar to those found in association with tumoral calcinosis.
calcification is a painful shoulder that corresponds anatomically to the insertion of the supraspinatus muscle onto the humerus.

Gross examination reveals amorphous chalky white deposits or circumscribed gritty calcifications. These deposits have been shown by x-ray diffraction studies to be hydroxyapatite crystals. Microscopic studies reveal calcium in fibrous or fatty tissue sometimes with associated chronic inflammatory cells including, at times, multinucleated giant cells.
### Accumulation of Abnormal Metabolic Products and Various Hematologic Disorders

#### Deposition and Storage Diseases, 212
- **Oxalosis**, 212
- **Amyloidosis**, 212
- **Gaucher’s Disease**, 214
- **Niemann-Pick Disease**, 218
- **Primary Hyperlipidemias and Xanthomatosis**, 218
- **Membranous Lipodystrophy, Lipomembranous Polycystic Osteodysplasia (Nasu-Hakola Disease)**, 220

#### Skeletal Manifestations of Hematologic Diseases, 220
- **Hemochromatosis**, 221
- **Sickle Cell Disease**, 222
- **Thalassemia**, 225
- **Myelofibrosis (Agnogenic Myeloid Metaplasia; Assmann’s Disease)**, 226

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Philippe Charles Ernest Gaucher (July 1854—January 1918). Gaucher is remembered for his description of the disorder that was to become known as Gaucher’s disease. In 1882, while still a student, he discovered this disease in a 32-year-old woman who had an enlarged spleen. He published his findings in his doctorate thesis titled "De l'epithelmoma primitif de la rate, hypertrophie idio-pathique de la rate sans leucemie." (From the Wellcome Library, London.)

Thomas Sydenham (1624—December 1689). Sydenham has been called the English Hippocrates, and the father of English medicine. Sydenham himself suffered with renal stones and gout, and published the most graphic descriptions of the disease from the perspective of the patient. (From the Wellcome Library, London.)

James Bryan Herrick (August 1861—March 1954). Herrick studied and taught at various Chicago, Illinois hospitals, including Cook County Hospital and Presbyterian Hospital. In 1908, he discovered sickle shaped red blood cells on the blood film of a medical student from Grenada. Later in his career, he postulated that thrombosis in the coronary artery led to the symptoms and abnormalities of heart attacks. (From Wild PS. Chicago Literary Club: Its History from the Season of 1924-1925 to the Season of 1945-1946. Chicago, printed for the club, 1947.)
Skeletal abnormalities characterized by the accumulation of metabolic products may complicate a number of genetic metabolic disturbances, some of which are discussed elsewhere. (Those in which the joint is most commonly affected, such as gout and calcium pyrophosphate deposition, are discussed in Chapter 12; the mucopolysaccharidoses are discussed in Chapter 6.)

The first part of this chapter discusses oxalic acid deposition, amyloidosis, and various lipid disturbances; the second part covers the effects of various hematologic disorders.

**Deposition and Storage Diseases**

**OXALOSIS**

Normally oxalic acid, an end-product of both amino acid and vitamin C metabolism, is excreted in the urine. However, in both primary and secondary oxalosis, calcium oxalate crystals may be precipitated into various tissues including bone, bone marrow, and cartilage.

Primary (familial) oxalosis is transmitted as an autosomal recessive trait and usually presents in early childhood, although in a few cases, its appearance may be delayed until adulthood. It is characterized by excessive biosynthesis of oxalate secondary to a deficiency of the peroxisomal liver-specific alanine: glyoxylate aminotransferase gene. The result is nephrolithiasis and secondary chronic renal failure. Deposition of calcium oxalate crystals in many tissues, including the bone and bone marrow, is a prominent feature.

Secondary oxalosis is more common. The setting is usually that of chronic renal failure and the degree of crystal deposition is generally much less severe than in primary oxalosis. In affected individuals, blood levels of calcium oxalate are elevated and correlate significantly with the serum creatinine value. Oxalate deposits may be seen in many organs including the kidneys, heart, thyroid, lungs, as well as bone, cartilage, synovium, and in the synovial fluid.

Radiologic evidence of disease in the skeleton depends on the severity of the condition and, therefore, is more often seen in primary oxalosis. In children, radiodense bands in the metaphysis may result from crystal deposition in growth arrest lines (Fig. 9-1).

Microscopic examination of skeleton tissue from both primary and secondary oxalosis may reveal crystals in mineralized bone, articular cartilage, or bone marrow. The crystals can be identified by polarized light microscopy, as highly refractile needle-shaped crystals that form star-like clusters (Figs. 9-2 to 9-4). Positive identification of the crystals can be achieved by chemical analysis, x-ray diffraction, or electron diffraction. (The latter technique offers a precise method for identification of extremely small quantities of calcium oxalate in bone biopsy specimens.) There is generally a lack of cellular response to the crystals; however, a mononuclear cell or a giant cell reaction similar to that seen in patients with other crystal deposition disorders may be present. (In the bone evidence of secondary hyperparathyroidism with increased osteoclastic resorption, as well as hyperosteoendosis, is also frequently seen and is to be expected in the setting of chronic renal failure.)

**AMYLOIDOSIS**

Amyloidosis is a heterogenous group of conditions characterized by the extracellular deposition of an amorphous protein material in various tissues, either systemically or locally. The amyloid deposits may be recognized by bright green fluorescence under polarized light after staining with congo-red, a regular fibrillar structure by electron microscopy, and a β-pleated sheet structure by x-ray diffraction. Amyloid associated with bone marrow disease, including multiple myeloma, results in systemic amyloidosis, or primary...
accumulation of abnormal metabolic products and various hematologic disorders

Amyloidosis that is composed of monoclonal light chain immunoglobulin. The type of amyloidosis associated with various chronic inflammatory disorders such as rheumatoid arthritis, psoriasis, Crohn’s disease, osteomyelitis, tuberculosis, and so on, which used to be known as secondary amyloidosis is composed of serum amyloid A protein.

Although skeletal involvement is probably not that uncommon, it is rarely recognized clinically. Some patients with amyloidosis may present with aching bone pain, a localized tumor or even multiple tumors, and pathologic fractures. Such patients are most likely to be diagnosed clinically with metastatic tumor, and the true nature of the disease does not become apparent until histologic examination is performed (Figs. 9-5 to 9-7).

An increasing frequency of carpal tunnel syndrome (CTS) in patients on long-term hemodialysis has been reported, with a correlation between the length of time on dialysis and the development of CTS. In these patients amyloid deposits formed of β2-microglobulin can usually be demonstrated in the synovial tissue. However, the amyloid may be difficult to distinguish microscopically from an excess of collagen tissue or hyalinized collagen. In such patients, deposits of amyloid may also be seen as localized destructive bone lesions around large joints, or often with bilateral involvement of multiple joints. Radiologic examination may reveal juxta-articular osteoporosis, extensive swelling of the soft tissues, multiple well-defined subchondral cysts, and pressure erosions from synovial hypertrophy. However, despite these changes, usually there is relative preservation of the joint space (Fig. 9-8).

Patients with diffuse marrow involvement usually show a predominantly axial distribution of amyloid and may have painful compression fractures that may mimic multiple myeloma. A localized lytic form of amyloidosis affecting the long bones, skull, or ribs is usually seen radiographically as one or more well-margined lytic lesions.
Microscopic examination of sections stained with hematoxylin-eosin (H&E) generally shows irregular fragments of a glassy eosinophilic material, sometimes with an adjacent histiocytic or giant cell response (Fig. 9-9). Histologic sections of amyloid deposits stained with Congo red have a characteristic apple green birefringence when examined under polarized lights. However, it should be noted that it may be difficult to recognize amyloid deposits when they occur in connective tissue matrix, because collagen, especially denatured collagen, also produces a similar apple green color when examined under polarized light (Fig. 9-10).

GAUCHER’S DISEASE

The so-called lipidoses encompass a wide variety of disorders in which congenital enzyme deficiencies lead to the accumulation of complex lipid compounds. By far the most common of these disorders is Gaucher’s disease.

There are three types of Gaucher’s disease that are inherited in an autosomal recessive fashion. These have been linked to particular mutations:

- Type I, the most common (N370S homozygote), occurs mainly in Ashkenazi Jews and about 1 in 15 of this population are carriers of the disease. It is usually diagnosed in late childhood or early adulthood. Life expectancy is mildly decreased. There are no neurologic symptoms.
- Type II, seen in small children (1 or 2 alleles L444P) is characterized by neurologic problems. Prognosis is poor; most die before reaching the third birthday.
- Type III (also 1 or 2 copies of L444P) occurs in Swedish patients from the Norrbotten region. This group develops the disease somewhat later, but most die before their 30th birthday.

The disease is caused by a defect in the gene lysosomal glucocerebrosidase (also known as β-glucosidase) that catalyses the breakdown of glucocerebroside, a cell membrane constituent of red and white blood cells. The macrophages that clear these cells are unable to eliminate the cell membrane waste product, which accumulates as intracellular fibrillar material. These macrophages are the Gaucher cells and appear on light microscopy to contain material that has been likened to crumpled up paper. They accumulate in the reticuloendothelial system, including the liver, spleen (splenomegaly may be dramatic), lymph nodes, and bone marrow (Fig. 9-11).

Patients who present with type II and III disease in infancy have an acute neuropathic form of the disease in which, during brain...
Figure 9-7  A, Radiograph of the skull in a patient with generalized primary amyloidosis shows multiple lytic areas, which originally suggested the presence of a myeloma. B, Radiograph of a portion of the pelvis and the right hip in the same patient illustrated in (A). Again multiple lytic lesions can be seen in the neck and shaft of the femur. In addition, a fracture has occurred through the femoral neck. C, Cut surface of the femoral head removed from the patient with pathologic fracture shown in (B). The lytic areas are represented by sites of bone destruction filled by a glassy pink tissue. D, Histologic section demonstrates that glassy areas are acellular deposits of amyloid (H&E, × 1 obj.). E, A higher power view shows the dense eosinophilic amyloid deposits with admixed fibroblasts and vessels (H&E, × 10 obj.).
Section III: Metabolic Disturbances

Development and the formation of the myelin sheath, cerebrosides accumulate within the brain.

Most patients with type I have a chronic form of the disease that pursues a benign asymptomatic course and that often is not diagnosed until the patient is adult. A common complication, especially in younger individuals, is avascular necrosis of the femoral head (Fig. 9-12).

In more severely affected type I patients, the long bones show on radiographs irregular thinning of the cortices, which gives them a trabeculated appearance. Frequently, the lower end of the femur, the upper end of the tibia, and the upper end of the humerus fail to remodel during development, leading to the Erlenmeyer flask...
deformity (Fig. 9-13). The spine usually exhibits loss of density, and frequently one or more of the vertebrae show collapse with either a wedge-shaped deformity, platyspondyly, or occasionally, fish-mouth deformities (Fig. 9-14). In less severely affected individuals, a nonspecific osteopenia is the only skeletal finding. Occasionally in a few patients, in addition to osteopenia, some osteosclerotic

**FIGURE 9-11** Gaucher’s disease: photomicrograph shows widespread replacement of the bone marrow tissue by sheets of pink cellular tissue. Some residual normal marrow is seen at the top of the frame (H&E, × 4 obj.).

**FIGURE 9-12** A. Photograph of frontal section through a femoral head removed from a middle-aged woman patient with Gaucher’s disease. The marrow is dark red with a diffuse spotty infiltrate of grayish yellow tissue. On the superior articular surface is a 1.5-cm wedge-shaped focus of scarring and necrosis. B. A radiograph of the specimen slice; note the fractures that have occurred at the margins of the necrotic area.

**FIGURE 9-13** Radiograph of the lower femur of a patient with Gaucher’s disease shows flaring of the metaphyseal region and distal diaphysis with a bubbly osteolysis of the affected bone.

**FIGURE 9-14** Radiograph of a patient with late stage Gaucher’s disease, osteopenia, and collapse of L1, L2, and L5.
lesions are also present. These areas of sclerosis probably result from infarction within the affected bone.

The skeletal alterations in Gaucher’s disease result from massive infiltration of the marrow space by large histiocytes, or Gaucher’s cells, that usually measure 40 to 80 µm in diameter and have a characteristic crumpled or wrinkled paper appearance of the cytoplasm (Figs. 9-15 and 9-16). Because the infiltration of the marrow space tends to compromise venous return, diagnostic bone biopsy may be complicated by secondary infarction and/or infection (Fig. 9-17).

NIEMANN-PICK DISEASE

Niemann-Pick disease, an autosomal recessive disorder, is characterized by an accumulation of sphingomyelin in the reticuloendothelial system.

The classic presentation of Niemann-Pick disease is that of a child dying before the age of 4 years with clinical findings of massive hepatosplenomegaly, foam cells in the bone marrow, and irreparable disordered of the nervous system. Postmortem examination reveals many lipid-laden histiocytes in nearly every organ of the body.

PRIMARY HYPERLIPIDEMIAS AND XANTHOMATOSIS

The presence of raised or abnormal levels of lipids or lipoproteins in blood is extremely common in the general population, as well as in familial type II hyperlipoproteinemia. Subcutaneous xanthomas and asymptomatic tendinous xanthomas are not uncommon. The most

**FIGURE 9-15** A, A photomicrograph of an infiltrate of Gaucher’s cells, which are seen to be swollen histiocytes with a foamy cytoplasm and a crinkled appearance. The infiltrate is replacing the normal bone marrow (H&E, × 10 obj). B, A higher power image of the Gaucher’s infiltrate (H&E, × 25 obj). C, Shows the size of the Gaucher’s cells relative to those of the bone marrow. Note also the cytoplasm of the Gaucher’s cell, which has been likened to crumpled tissue paper (H&E, × 40 obj).

**FIGURE 9-16** Radiograph of the humerus of a patient with Gaucher’s disease complicated both by osteomyelitis and infarction. Note the linear marrow calcification so characteristic of infarction.
common sites for tendinous xanthomas are the Achilles tendon (Fig. 9-18) and the extensor tendons of the fingers, where the lesions are likely to be bilateral and symmetrical. Occasionally, the plantar fascia is found to be infiltrated with xanthoma cells.

The nontender masses in the tendons are generally only of cosmetic concern, although very occasionally associated tendinitis develops. Very rarely patients may complain of an acute transient arthritis of one or more joints.

Gross examination of tissue obtained from an affected site generally shows a bright yellow nodular lesion, which on microscopic examination reveals packed lipid-laden histiocytes, often with cholesterol clefts.
Membranous Lipodystrophy, Lipomembranous Polycystic Osteodysplasia (Nasu-Hakola Disease)

A very rare disturbance in lipid metabolism, affecting both the skeleton and the central nervous system, has been described mainly in Japan and Finland, although the disease is not exclusively found in these races. The affected individuals are generally in their teens or early 20s at the time of diagnosis and both sexes are affected.

The patients may initially present with bone pain or pathologic fracture, usually in the hands or feet or around major joints. Later neurologic symptoms such as ataxia, tremor, urinary incontinence, or psychiatric disease such as paranoia or even early onset dementia occur. The outcome is usually early death during the fifth decade.

Radiographs show well-defined cystic lesions with sclerotic margins in the metaphysis of long bones and in carpal or tarsal bones. Radiographically, the axial skeleton is generally not affected (Fig. 9-19).

Microscopically in the affected areas, the fatty bone marrow is replaced by characteristic membranous lined cysts, which have a markedly papillary and folded appearance. (Because occasionally similar membranous structures are very occasionally seen in ischemic fat in association with other conditions, the diagnosis of Nasu-Hakola disease is therefore dependent not only on the histology but also on the clinical presentation [Fig. 9-20].)

Recently, molecular analysis of affected families has revealed mutations in the DAP12 (TYROBP) or TREM2 genes. This provides an interesting example of how mutations in two different subunits of a multisubunit receptor complex may result in an identical human disease phenotype.

Skeletal Manifestations of Hematologic Diseases

Various hematologic conditions such as the hemolytic anemias, hemoglobinopathies, and bleeding diatheses often lead to bone disease or joint damage. (Joint destruction secondary to chronic bloody synovial effusions as seen in patients with hemophilia is considered in Chapter 12.)

Changes in the cancellous bone are generally secondary to either erythroid hyperplasia, as seen in patients with thalassemia and the hemolytic anemias, or vascular thrombosis with subsequent infarction and infection, as seen in patients with sickle cell disease.

The severity of disease seen radiographically depends, to a certain extent, on the age of the patient at presentation, with children often more dramatically affected.

Location also varies with age. In patients who manifest chronic hematologic disease during infancy, the hands and feet show marked skeletal alterations, whereas in slightly older children, the skull may be the predominant site. In the mature skeleton of an adult the most dramatic changes usually affect the pelvis and the spine.
Primary hemochromatosis is one of the most common inheritable genetic defects, especially in people of northern European extraction, with about 1 in 10 people carrying a mutation in one of the genes regulating iron metabolism. Five types of disease based on different gene mutations have been recognized, all but one of which are recessive. Increased iron absorption is associated with the accumulation of iron in various tissues. Early recognition and treatment of this condition can help prevent significant organ damage. (Excessive iron accumulation [usually of the visceral organs and in particular, the heart and liver] may also be caused by massive oral iron intake or by severe chronic hemolytic anemia that requires protracted courses of transfusion therapy. The resulting disease is known as secondary hemochromatosis, and this is probably the most common form of the condition.)

Patients with hemochromatosis often first present when they are in their 50s with liver disease. When younger patients present, the disease is usually more severe.
In general, the radiographic changes in the bones and joints in hemochromatosis are nonspecific and are best characterized as a noninflammatory arthropathy, classically with involvement of the metacarpophalangeal joints, especially the second and third (Fig. 9-21). Less commonly, large joints, such as the shoulder and elbows (a distribution that is atypical for classic osteoarthritis), are involved (Fig. 9-22). There may be regional osteoporosis as well as peculiar cysts and erosions around the affected joints. Of interest is the associated high incidence of chondrocalcinosis in patients with hemochromatosis (15% to 30%), which is usually attributed to interference by iron with the enzymatic degradation of pyrophosphates (Fig. 9-23). Grossly the disease may be recognized by a generalized mahogany brown coloration of the tissues, which is reflected microscopically as an accumulation of hemosiderin pigment (Fig. 9-24). Treatment should be directed at the underlying disorder that is causing the accumulation of iron.

(The brown discoloration of the joint tissue classically seen in patients with this disorder may easily be confused with local iron deposition from extravasated blood, as seen in patients with traumatic arthropathy or hemophilic arthropathy.) (See also Chapter 12.)

**SICKLE CELL DISEASE**

A number of hematologic diseases result from the formation of abnormal hemoglobin; these conditions are known collectively as the hemoglobinopathies. In sickle cell disease, a point mutation in the β-globulin chain of hemoglobin results in a substitution of the amino acids glutamic acid, with the less polar amino acid valine. In conditions of low oxygen tension, this causes crystallization of the hemoglobin molecule, which, in turn, results in formation of abnormal sickle shaped erythrocytes and subsequent hemolysis. The hemolytic anemia, in turn, leads to bone marrow hyperplasia.

Sickle cell disease is practically limited to blacks, and it is estimated that about 8% to 10% of blacks have the sickle cell trait (the heterozygous form of sickle cell hemoglobinopathy); however, only about 0.15% have sickle cell anemia (the homozygous form of the disorder). Carriers of the disease, that is, those with sickle cell trait, have symptoms only when deprived of oxygen (high altitudes or under conditions of dehydration).

In those patients with sickle cell anemia who survive into later childhood and adulthood, the clinical course is characterized by alternating exacerbations and remissions. During the remissions, there is persistent anemia, a slight icteric tint of the sclerae, and evidence of sickling of the red blood cells. At unpredictable intervals, there is exacerbation of the disease process (a crisis), during which the anemia may become gradually or rapidly worse. This is characterized by rapid destruction of erythrocytes, with associated fever, increased icterus, nausea, vomiting, abdominal pain, and severe prostration. The crisis is often precipitated by an infection, especially in relation to the respiratory tract.

Other clinical features of the disorder include enlargement of the liver, initial enlargement of the spleen (this usually is seen only in the younger patients since later the spleen shrinks due to repeated infarcts), cardiac hypertrophy, recurrent chronic ulcers of the legs (especially in the region of the ankles), and episodes of severe pain secondary to local infarctions in the viscera, or bones and joints.

Radiologic examination of the skeleton may reveal generalized osteoporosis in the spine, often associated with vertebral
collapse, wedge-shaped deformities, and kyphoscoliosis (Fig. 9-25).

Characteristic changes may also be observed in the phalangeal bones of the hands and feet following infarcts that develop in infancy and interfere with normal growth (Fig. 9-26).

A serious problem in sickle cell disease is the development of infarcts, which may occur in any organ but notably in the spleen. In the skeleton, the infarcts may be located anywhere, although they are frequent in the hands and feet, as well as in the femoral head and spine (usually the lower spine). Infarction is often heralded by severe and sudden pain which may awaken the sleeping patient. Initial radiographs are normal, with infarct-related x-ray changes developing only after some months (see Chapter 15).

In addition to compression fractures and wedging fractures secondary to osteoporosis, the spines of affected children may also

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**FIGURE 9-24**

A. Photograph of the articular surfaces of the knee joint of a patient with hemochromatosis. The black-green staining of the cartilage results from the accumulated blood pigment, which eventually interferes with chondrocyte function and hence cartilage matrix metabolism. (Note: the gross and microscopic changes in hemochromatosis are similar to those seen in hemosiderosis. See Fig. 12-68A.)

B, Section through the femoral condyle shows separation of the necrotic articular cartilage from the underlying bone.

C. Photomicrograph of the articular cartilage of the femoral condyle shows extensive chondrocyte necrosis and heavy iron staining at the surface (Prussian blue, × 4 obj.).

D. Higher power shows iron staining within the chondrocytic lacunae (Prussian blue, × 25 obj.).

E. Photomicrograph demonstrates hemosiderin within the chondrocytes (H&E, × 50 obj.).

(Continued)
Figure 9-24—Cont’d  F, Photomicrograph of synovial membrane shows heavy hemosiderin deposition together with mild chronic inflammation and hypervascularity (H&E, × 10 obj.). G, Same section stained with Prussian blue stain shows extent of iron deposition (× 4 obj.). H, Higher power photomicrograph of the synovium (H&E, × 25 obj.).

Figure 9-25  Lateral radiograph of the spine of an adolescent black man with sickle cell disease. Note the mild osteopenia, with accentuation of the vertical trabeculae, and the central collapse of the vertebral bodies in the upper and midthoracic spine.

Figure 9-26  Radiograph of the hand of a patient with sickle cell disease. The shortening of the first metacarpal and of some of the phalanges is secondary to growth disturbances following sickle cell crises in infancy.
exhibit a double concavity resulting from collapse of the central portion of the vertebral body under the hyaline growth plate. Rather than being compression fractures caused by mechanical failure, it has been suggested that these lesions are the result of relative ischemia in this region of the vertebral body.

On macroscopic examination, the bones show a congested, dusky red appearance, indicative of marked erythroid hyperplasia of the marrow (Figs. 9-27 and 9-28). Microscopically, the erythrocytes themselves are deformed and often crescent shaped, which gives rise to the term sickle cell (Fig. 9-29). There may be profound osteoporosis because of marrow impingement on the adjacent trabecular bone structure.

Osteomyelitis is well-recognized complication of sickle cell disease, and this condition is usually the result of infection with *Staphylococcus aureus*. However, in some cases, it is due to infection with the *Salmonella* organism (Fig. 9-30). In the past, this complication often necessitated amputation of the involved extremity (Fig. 9-31).

**THALASSEMIA**

Thalassemia is inherited as a recessive condition that produces a deficiency of α- or β-globin in hemoglobin. Patients with homozygous β-thalassemia are usually severely anemic. Marked marrow hyperplasia (mainly due to erythroid hyperplasia) is associated with profound osteoporosis, and the radiographic changes in children are evident mainly in the skull, long bones, and metacarpals and metatarsals. As the patient matures, there is less involvement of the peripheral skeleton.

In general, the long bones show medullary widening with cortical thinning, often with development of saber shins. Involvement of the spine is usually manifested as kyphosis or scoliosis, which results from vertebral collapse. There may be a dramatic widening of the diploic space of the skull, with thinning and displacement of the trabeculae, producing a hair-on-end appearance (Figs. 9-32 and 9-33). The hands and feet may exhibit medullary widening and cortical thinning of the metacarpals and metatarsals, which appear on radiographs as a honeycomb pattern (Fig. 9-34). Involvement of the maxillary bones and sinuses may lead to a peculiar rodent facies. (Although osseous changes may also be observed radiographically in patients with the mild forms of thalassemia, they are usually much less severe.)

Grossly, the bones appear dusky red and are markedly osteopenic (Fig. 9-35). Microscopic examination of bone tissue from severely

**Figure 9-27** Photograph of a frontal section through the femur of a child who died from the complications of sickle cell disease. Note the dusky reddish brown appearance of the hyperplastic packed marrow.

**Figure 9-28** Histologic section of a vertebral body from a child with sickle cell disease. The marrow space is entirely filled with hematopoietic tissue, and there is very little fat evident. (Normally the marrow is 50% fat and 50% hematopoietic tissue. Many of the cleared areas seen in the bone marrow in this section are artifactual.) Osteoporosis is also present (H&E, × 1 obj.).

**Figure 9-29** A, Photomicrograph demonstrating sickle cells in blood clot (H&E, × 25 obj.). B, Sickled red cells within the lumen of a blood vessel. (Nomarski differential interference contrast microscopy, H&E, × 100 obj.).
affected patients reveals dramatic hyperplasia of the marrow, especially of the erythroid components and marked osteopenia. Perl’s Prussian blue staining demonstrates marked iron deposition in the bone marrow as well as in zones of mineralization and cement lines (Fig. 9-36).

Occasionally, thalassemia is seen in association with sickle cell disease, and in such cases, infarcts may be superimposed on the other symptoms.

**MYELOFIBROSIS (AGNOGENIC MYELOID METAPLASIA; ASSMANN’S DISEASE)**

Myelofibrosis, a relatively uncommon disease, is characterized by a diffuse fibrous replacement of the marrow with an associated granulocytic hyperplasia of the hematopoietic elements and the slow development of extramedullary hematopoiesis. The disease occurs with about equal frequency in men and women, and is more common clinically among older individuals. It is usually reactive following other myeloproliferative disorders such as polycythemia vera or essential thrombocytosis. The symptoms are progressive anemia and hepatosplenomegaly.

On radiographic examination, in approximately 50% of cases, the bones, particularly of the axial skeleton, show a diffuse but occasionally patchy sclerosis. The bony sclerosis, in combination with the marrow fibrosis, accounts for the frequency of dry taps when marrow aspiration is attempted. Approximately half of all adult patients exhibit dramatic involvement of the spine, pelvis, ribs, sternum, proximal humerus, and femur (the common sites of adult hematopoiesis) (Fig. 9-37). The skull is rarely involved. The involved bones are not expanded, and there is no change in their contour. The differential diagnosis is usually not difficult because of the diffuse sclerosis that occurs in this condition. Rarely, this disease may be closely mimicked by some cases of...
metastatic carcinoma and the rare osteosclerotic form of myelomatosis. Rare cases of spinal cord compression resulting from an extradural mass of hematopoietic tissue have been reported. About 20% of patients with myelofibrosis eventually develop acute myelogenous leukemia.

Microscopic examination of the marrow shows obliteratorive fibrosis in the late stages. In early stages, marked marrow hyperplasia and bizarre cell types may be seen, as well as an increase in reticulum fiber production. When viewed with polarized light, the thickened bone may be found to have a largely woven appearance.

**Figure 9-33** Radiograph of the skull of a patient with thalassemia major shows characteristic hair-on-end appearance.

**Figure 9-34** Radiograph of the hands in a patient with thalassemia shows severe osteoporosis with a honeycomb and cystic pattern of the cancellous bone.

**Figure 9-35** A, Segment of the vertebral column from a young patient with thalassemia major. The bone marrow is mahogany brown in color. B, Radiograph of the specimen reveals marked osteopenia.

**Figure 9-36** Thalassemia: photomicrograph of a section of bone stained with Perls' stain, which stains iron a blue color, shows the location of iron at the mineralization front (x 25 obj.).
FIGURE 9-37 A, Close-up photograph of the cut surface of a portion of the lower thoracic spine of a patient with myelofibrosis, to show the pale appearance due to the fibrotic replacement of the bone marrow. Note the lack of any deformity in the contours of the vertebral bodies. B, Photograph of a sagittal section through the macerated lumbar spine. Note the extremely sclerotic bone associated with this condition. A radiograph (C) of the same specimen shows patchy osteosclerosis, with a complete loss of the normal trabecular pattern. A specimen radiograph (D) of a 2-mm slice through one of the vertebrae demonstrates more clearly the mottled sclerosis and loss of trabecular pattern seen in this condition. Photomicrograph (E) shows a section of bone from one of the vertebral bodies. Note that there is extensive new bone formation, as well as fibrosis of the marrow space with displacement of hematopoietic tissue. The same specimen photographed with polarized light.
FIGURE 9-37—CONT'D  (F) shows that the extensive new bone formation has an immature or woven pattern (H&E, × 10 obj.). G, A higher power photomicrograph to demonstrate marrow fibrosis, focal erythroid hyperplasia, and atypical myeloid cells (H&E, × 25 obj.).
The Dysfunctional Joint

Alexander Ogston (April 1844—February 1928). The eldest son of Francis Ogston, professor of medical jurisprudence in the University of Aberdeen, Alexander Ogston took his MB, ChB at Aberdeen with honors in 1865, and 1 year later received his doctorate. Later he studied abroad at Prague, Vienna, Berlin, and Paris. In 1882, Ogston became Regius Professor of Surgery at Aberdeen, a post that he held with great distinction for 27 years. He is best remembered as the discoverer and name of Staphylococcus aureus, which he recognized was the cause of abscess formation. His studies on joints, ‘The growth and maintenance of articular ends of adult bones’ (J Anat Physiol 1878), is fundamental to the understanding of joint anatomy. (From the Wellcome Library, London.)

Thomas Walmsley (1889—March 1951). Walmsley was professor of anatomy in The Queen's University of Belfast. He was educated at Glasgow University and graduated in medicine in 1912. In 1916, he was awarded the MD degree with honors, and was Bellahouston Gold Medalist for his thesis on joints and their mechanisms, an interest that was to persist throughout his life. The importance of Walmsley’s studies toward an understanding of joint mechanics cannot be overestimated. (In Memoriam: Thomas Walmsley, M.D., F.R.S.E. 1889-1951. [no authors listed]. J Anat 1952;86[Pt 2]:226-228.)
To a man who does not understand the workings of a machine, it naturally seems, when he sees it in operation, that the most important part of the machine is the chip of wood that accidentally got into it and is tossed about in it, interfering with its working. A man who does not know the construction of the machine cannot understand that it is not this harmful and interfering chip of wood, but that little transmission gear turning noiselessly that is one of the most essential parts of the machine.


The major business of orthopaedic surgeons, rheumatologists, physiatrists, chiropractors, osteopaths, masseur therapists, and many others, is the treatment of “arthritis,” a disease state that few of us escape.

In the simplest terms, an arthritic joint is a broken joint. Again in the simplest terms, a joint is a hinge, and if you have ever tried to deal with a simple broken door hinge, you quickly realize that you need to know how it works before you can fix it. From all of those hours spent in the dissecting room as a student, it is hoped that one comes out realizing that joints are awfully complicated hinges and that only two of them are ever exactly the same: the one on the right side and the one on the left side, which are more or less mirror images of each other. The bioengineers have discovered that creating an artificial joint or artificial tissue that works like the real thing is not easy.

Joint dysfunction (arthritis) is characterized clinically by instability, loss of motion, maldistribution of load, and associated pain. Conversely, normal joint function is characterized by: the maintenance of stability during use; freedom of the opposed articular surfaces to move painlessly over each other within the required range of motion; and correct distribution of load across joint tissues, which might otherwise be damaged by overloading or become atrophied because of habitual underloading (disuse).

The particular function of each joint is fulfilled by the architecture of that joint and the mechanical properties of the matrices of the connective tissues of which the joint is constructed. An intact neuromuscular control of the joint is essential.

Function and Anatomy

The three interdependent aspects of joint function (stability, motion, and load distribution) depend on three major anatomic features.

GEOMETRY OF OPPOSED ARTICULATING SURFACES OF THE JOINT

Perhaps the most obvious feature of any joint is its unique shape. In general, one joint surface is convex, whereas the other is concave. The convex, or male, side of the joint usually has a larger articular surface than the concave, or female, side. The female side of the joint is often augmented by a pliable dense fibrous component, such

FIGURE 10-1 The physiologic incongruity between the articular surfaces also allows access for the synovial fluid, which is important for both nutrition and lubrication.

as the labrum of the hip or the menisci of the knee, which have an important role in normal function. The complementary shapes of the surfaces are necessary to permit the normal range of motion for that particular joint as well as to provide stability and ensure the most equitable loading during use (Fig. 10-1).

At first sight in some joints (for example, the hip and the ankle), the articular surfaces appear to fit very exactly (i.e., they appear congruent). However, in other joints (e.g., the knee and finger joints), it is readily apparent that the surfaces are incongruent. For a long time, it was believed that congruence (exact fit) was a normal feature of a joint. However, the concept of congruence in all positions of the joint would imply that joint surfaces were perfectly spherical, perfectly cylindrical, or perfectly flat, which they are not, and therefore, no normal joint can be congruent in all positions, although it may be more congruent in one position than in another.

In many joints, of which the knee is a notable example, the gross incongruence of the opposed surfaces is partially compensated for by the interposed, pliable intra-articular fibrocartilaginous menisci. (These latter structures constitute an important component contributing to joint shape and function and cannot be removed without significant consequences [Fig. 10-2].)

Because the tissues of a joint undergo elastic deformation under load (particularly the cartilage but also the bone), as the load increases, the surfaces of the joint come into increasing contact, thereby distributing the load more equitably (Fig. 10-3). Both the incongruence and the deformation of the joint space under loading conditions provide for the circulation and mixing of the synovial fluid essential to the metabolism of the chondrocytes.

MECHANICAL PROPERTIES OF EXTRACELLULAR MATRICES OF BONE, CARTILAGE, AND OTHER CONNECTIVE TISSUES

Most investigators since William Hunter have recognized the importance of the articular cartilage to joint physiology. As Hunter noted
in 1743, 'the articulating cartilages are most happily contrived to all purposes of motion in those parts. By their uniform surface, they move upon one another with ease; by their soft, smooth and slippery surface, mutual abrasion is prevented; by their flexibility, the contiguous surfaces are constantly adapted to each other and the friction diffused equally over the whole; by their elasticity, the violence of any shock, which may happen in running, jumping, etc. is broken and gradually spent; which must have been extremely pernicious, if the hard surfaces of bones had been immediately contiguous.' Hunter, in these few sentences, perfectly summarized the function of cartilage. However, it needs to be also recognized that the mechanism of the joint includes the bone beneath the cartilage, the ligaments that conjoin the articular bone ends, and other structures besides. Alterations in the mechanical properties of bone or disruption of the ligaments may have equally disastrous effects on joint function as alterations in cartilage properties.

The physical properties of connective tissues are determined by their extracellular matrices. In each of the different connective tissues, as well as in each particular structure, the matrices have a unique composition and organization that provide for mechanical function at that locus. Some of the details of this organization are discussed in Chapter 1.

The connective tissue matrices are both synthesized and broken down by their intrinsic cells (e.g., osteoblasts, osteocytes, osteoclasts, chondrocytes). In maintaining the physicochemical and mechanical properties of tissues, the function of these cells must be subject to highly sensitive feedback systems involving both local and systemic factors, which are only now beginning to be studied (Fig. 10-4).

**INTEGRITY OF LIGAMENTS, MUSCLES, AND TENDONS SUPPORTING THE JOINT AND THEIR NEUROMUSCULAR CONTROLS**

Functional joint anatomy must include a consideration of the ligamentous conjoining of the articulating surfaces as well as of the neuromuscular control of joint motion. Sensory feedback monitors our movements through the perception of touch, temperature, pain, and position. During childhood, we explore, learn, practice, and perfect skills that will eventually become automatic. The fact that some of us develop better athletic skills than others is perhaps not as dependent on strength and endurance as it is on optimization of the sensory modulation of movement. Correct joint function is thus dependent on intact ligaments and neuromuscular coordination (Fig. 10-5). As recognized by Charcot in the 19th century, a breakdown of neuromuscular coordination can lead to profound arthritis.
Arthritis

Normal Joint Physiology

Anatomy is concerned with the structure of living things; physiology is concerned with their normal dynamic phenomena. Wolff’s law states that bone density and bone architecture correlate with the magnitude and direction of applied load. In the articular end of a bone, this implies that the subchondral bone trabeculae must also undergo a self-regulated modeling that maintains a joint shape capable of optimal load distribution. In other words, the shape of bones, including the articular ends, reflects a dynamic state that also incorporates a feedback dependent on mechanical stress.

One mechanism that provides for both growth and bone modeling is endochondral ossification. This process is exemplified in the epiphyseal growth plate, where calcified cartilage is invaded by blood vessels from the metaphyseal bone and replaced by bone tissue synthesized by osteoblasts lying close to the invading blood vessels (see Chapter 1). Studies of adult joints have shown that replacement of the calcified layer of articular cartilage by bone tissue involves a similar process.

Blood vessels from the subchondral bone penetrate the calcified zone of the articular cartilage, and alongside the channels, which are created by this process, new bone is laid down; thus the calcified cartilage is slowly replaced by new subchondral bone (Figs. 10-6 and 10-7). Replacement of the calcified layer of cartilage by bone might be expected to result in its eventual disappearance. However, histologic study of articular cartilage from subjects of various ages shows that this does not happen. The thickness of the calcified zone of articular cartilage remains much the same throughout life because the calcification front (tidemark) continues to advance into the noncalcified cartilage at a slow rate that is in equilibrium with the rate of replacement from the subchondral bone. Therefore a priori, articular cartilage is not a static tissue as it was long believed to be. The extracellular matrix and the chondrocytes are replaced throughout life, and the joint undergoes continuous remodeling (see also Fig. 1-56).

Heterogeneity of cartilage tissue including both morphologic and biochemical variations can be observed within different regions of a normal weight-bearing joint. For example, there is a variation in stiffness in different areas of the femoral head that has been related both to proteoglycan (PG) content and to the amount of water held by the tissue.

Another example of normal geographic variation can be observed in the tibial plateau of humans as well as other animals, where there are distinct morphologic differences between articular cartilage that

FIGURE 10-4 Diagrammatic representation of a chondrocyte to show some of its metabolic functions. In this diagram, the anabolic activity of the chondrocyte is stressed, but the chondrocyte also has a catabolic role, producing substances that break down the cartilage matrix.

FIGURE 10-5 A joint should be thought of not only in terms of the articular cartilage and synovial lining but also as a mechanical system, which includes all the surrounding ligaments, tendons, sensory and motor nerves, and muscles.

FIGURE 10-6 The articular cartilage is locked to the underlying bone by a layer of calcified cartilage. The edge between the articular cartilage and the calcified zone is marked by a basophilic line—the tidemark. With accelerated rates of calcification, many tidemarks may be present, and unless ossification of the calcified zone takes place, the calcified layer will become thicker (H&E, ×25 obj.).
is covered and that is not covered by the meniscus. These differences consist of a rough surface and soft matrix in the uncovered area as compared with the smooth, firm areas covered by the menisci. We have examined adult human as well as dog knee joints at autopsy and found that articular cartilage not covered by meniscus always showed matrix softening and superficial fibrillation. The morphologic and biochemical findings in these two distinct articular areas as studied in the adult dog are summarized in Figure 10-8.

We hypothesize that these naturally occurring variations in matrix structure and mechanical properties are related to joint loading experienced in normal everyday use. In the normally functioning knee, load is transmitted through the meniscus and onto the tibial cartilage underlying the meniscus, whereas the exposed cartilage that is not covered by the meniscus remains relatively underloaded. Other similar areas of possible disuse atrophy have been described around the rim of the radial head, in the roof of the acetabulum, and on the perifoveal and inferomedial aspects of the femoral head.

The extracellular matrix of the cartilage and of the other connective tissues is synthesized by their intrinsic cells under the control of both local and systemic factors. Both in vivo and in vitro studies have demonstrated that changes in the immediate environment of the joint lead to alterations of the cartilage matrix. Thus, immobilization or unloading of a joint results in decreased synthesis of glycosaminoglycans (Fig. 10-9). Conversely, exercise appears to increase synthesis. These experimentally induced variations are in agreement with naturally observed topographic variations in joints that have been ascribed to normally occurring patterns of loading that affect the joints. In general, it seems that low levels of mechanical stress (i.e., below the physiologic range) are associated with enhanced catabolic activity, whereas stress within the physiologic range is associated with increased anabolic activity. Under conditions of supraphysiologic stress, the chondrocytes are unable to adapt. In other words, there is a window of physiologic stress above or below which the chondrocytes cannot maintain an adequate functional matrix (Fig. 10-10).

Although a number of substances have been implicated in the transduction of mechanical stimuli to metabolic events, the exact mechanism remains unclear.

The Pathophysiology of a Dysfunctional Joint

Arthritis is the clinical term used to describe the consequences of a breakdown in the joint’s normal function. These dysfunctions include loss of capacity for the articulating surfaces to move over one another easily, loss of joint stability, and, almost always, pain.

The loss of freedom of motion is usually associated with a change in joint shape and alterations in the tissue matrices themselves, which, in turn, affects their mechanical properties. Instability may result from alterations in ligamentous support and neuromuscular control. Pain may have a variety of sources: it may originate in the bone as a result of maldistribution of load; in the synovium as a result of reactive synovitis; or in the muscle as a consequence of reflex spasm.

Therefore, it follows that malfunction of a joint can be caused by acute or chronic injuries that produce either:
- Anatomic alterations in the shape of the articulating surfaces, for example, a fracture (Fig. 10-11), or alteration in the rate of bone modelling (Paget’s disease, hyperparathyroidism).
- Loss of integrity of the cartilage matrix or support structures around the joint, for example, by infection or immunologically mediated inflammation or mechanical injury of articular cartilage, ligaments, tendons, or capsular tissue.
- Alterations in the mechanical properties of the tissue matrices making up the joint, due to disturbances affecting matrix synthesis (e.g., ochronosis).

During the past century, on the basis of their characteristic clinical presentations and their morbid anatomy, several forms of arthritis have been well delineated. These include the infectious arthritides, both granulomatous and pyogenic; metabolic arthritis (e.g., gout and ochronosis); and the various rheumatic syndromes that have been classified according to their clinical and immunologic characteristics. Histologically, these rheumatic inflammatory arthritides show a destructive pattern but may be difficult to differentiate from each other solely by microscopic examination.

However, even when these various etiologies have been considered, there remain an enormous number of cases of arthritis affecting especially certain small joints of the hands and feet and some larger joints, of which the hip and knee are particularly commonly involved. These cases, which run a chronic course, are not primarily inflammatory and usually occur in older individuals. The clinical presentation and morbid anatomy in these cases are similar enough for all of them to be classified under the general appellation of osteoarthritis (OA). In the majority of cases, the etiology has been poorly understood, although mechanical injury is believed to be the most likely culprit.
MORBID ANATOMY OF THE ARTHRITIC JOINT

Shape
A change in joint shape, resulting from cartilage and bone loss, is a characteristic result of the inflammatory arthritides, that is, infection and rheumatoid arthritis (RA). However, in OA, although bone and cartilage loss may play an important part in the process, it is the addition of new bone and cartilage in the form of osteophytes, particularly at the joint periphery and sometimes beneath the articular surface, that is the most characteristic feature of the disease (Fig. 10-12).

Tissue Alterations
Before discussing the gross and microscopic findings in the cartilage, bone, and synovial tissues of arthritic joints, perhaps it is necessary to emphasize the following:

- Pathologic degeneration is defined in the Oxford Dictionary as ‘a morbid change in the structure of parts, consisting in a disintegration of tissue, or in a substitution of a lower for a higher form of structure’ (Sydenham Society Lexicon of Medicine and the Allied Sciences).

- Observed degenerative alterations in all tissues (including bone and cartilage) occur:
  - Normally as a result of aging—a change in the degree of hydration, color changes, changes in tissue elasticity.
  - As a result of disuse (inactivity).
  - As a result of abuse (injury).

- Regardless of the cause, joint trauma is characterized by certain basic cellular and tissue responses. There is usually macroscopic and microscopic evidence of both injury and repair, and there are alterations both in the cells and most obviously in the extracellular matrix. (The changes in the extracellular matrix may result from direct mechanical physical injury, or alteration in the cellular synthesis of the matrix, or from enzymatic breakdown of the matrix.)

- In vascularized tissues, all injury, whatever its cause, is followed by an acute and then a chronic inflammatory response. As a result, the necrotic injured tissue is removed and replaced by proliferative vascular tissue (granulation tissue), which, in turn, results in repair of the injured tissue by fibrous scar. Independently of scarring, a second mode of repair involves regeneration of tissue similar to that which was injured originally.

FIGURE 10-8 Summary of morphology and biochemistry. A, In the covered area of the tibial plateau, the surface is smooth and covered by an amorphous electron-dense layer. The chondrocytes are flattened (H&E, × 4 obj.). With respect to lipid, there is an increased intracellular accumulation in all three layers, an increased extracellular matrix lipid accumulation at the surface, and increased numbers of extracellular matrix vesicles in the deep zone. B, Collagen appears in the electron microscope as randomly oriented fibers with thicker mean diameters; there is regular binding of proteoglycan (PG) to the collagen fibers, and the concentration of PG per wet weight is increased. C, In the uncovered area, the surface is irregular, with a detached electron-dense layer. The cells are round (H&E, × 10 obj.). D, Collagen appears in wavy aggregated bundles with thinner mean diameters (small range). PG can be more easily extracted from the matrix. In both the covered and the uncovered areas, there is the same amount of DNA per dry weight of cartilage tissue.

(Continued)
FIGURE 10-8—CONT'D E. Summary diagram of the differences in loaded and unloaded cartilage. Note that in the covered area the tidemark is irregular, whereas in the uncovered area the tidemark is smooth.

FIGURE 10-9 A. This dog had a distraction device placed across the left knee joint to produce unloading of the joint. B. Photomicrograph of articular cartilage harvested from the unloaded joint, demonstrating diminished proteoglycan staining. In C, a portion of normal control cartilage from the right knee is shown for comparison (Alcian blue stain, × 4 obj.). In B and C, the articular surface of the cartilage is seen at the right side of the photomicrograph and the deep portion at the left.
In nonvascularized tissue, such as cartilage, an inflammatory response and subsequent scarring cannot occur; however, this does not preclude tissue regeneration. (Note, however, that cartilage injury always eventually invokes an inflammatory response, because some vascularized tissues, such as bone and/or synovium, are inevitably involved in the process.)

**Cartilage Injury and Repair**

Macroscopic evidence of injury to cartilage is evident only in the extracellular matrix, mainly the collagenous component, and one
of the earliest visible findings is a disruption of the surface, which, instead of being smooth, becomes rough or eroded.

Three visible patterns of collagenous injury can be identified: surface fibrillation, cracking, and erosion (ulceration).

The term fibrillation is used to describe replacement of the normally smooth, shiny surface by a surface similar to cut velvet (Fig. 10-13). This type of transformation can be observed both on very thick cartilage, such as the patella, and on very thin cartilage, such as that found in the interphalangeal joints. The pile of the fibrillated area may be short or shaggy. The junction between the fibrillated area and the adjacent normal-appearing cartilage is usually well defined and generally distinct.

There appear to be two patterns of fibrillation. Well-defined areas of fibrillation affect particular locations in certain joints and are present in everyone from an early age. It is suggested that these areas are related to underloading of the cartilage. In osteoarthritic joints, there are areas of fibrillation that appear in different areas and that appear to be secondary to mechanical erosion of the cartilage surface. The microscopic characterization of these two distinct types of fibrillation is incomplete, but perhaps the latter is distinguished by deeper clefts and when examined microscopically a greater tendency to form cartilage clones.

Cartilage erosion, or solution of the surface, is characteristic of progressive injury in the joint. The base of the erosion appears initially to be either contoured or smooth. Tissue damage may eventually be so extensive as to completely denude the bone surface of its cartilage cover (eburnation) (Fig. 10-14).

The last form of structural lesion in this group, which is distinctly less common than either fibrillation or ulceration, is cracking of the cartilage. These cracks extend vertically deep into the cartilage and microscopically often have a deep horizontal component (Fig. 10-15).

In considering the pathogenesis of these three histologic types of cartilage matrix damage, it is important to recognize that in the early stages of arthritis, the damage may affect the opposed articular surfaces in different areas and to different degrees (Fig. 10-16). This is in marked contrast to eburnation, in which both of the opposed surfaces are affected. Therefore, it appears that in many cases fibrillation and other cartilage alteration cannot be solely ascribed to wear and tear as the opposed articular surfaces move over each other.

An increase in the ratio of water to PG in the cartilage matrix leads to softening of the cartilage (chondromalacia (Figs. 10-17 and 10-18). Chondromalacia and fibrillation usually occur together, but chondromalacia may be present before there is any obvious gross evidence of fibrillation.

Cellular injury is recognizable only under a microscope. Necrosis can be identified when only the ghost outlines of the chondrocytes remain. This ghosting, usually scattered but focal in distribution, is a
FiGURE 10-16  A, Photograph of the superior surface of the right femoral head removed from an 86-year-old man. Note the generally smooth, intact articular surface. However, there is a superficial ulcer adjacent to the fovea and some roughening around the periphery of the femoral head. This photograph should be compared with B. B, The acetabulum of the hip joint shown in A demonstrates superficial erosion and fibrillation of the articular cartilage in the superolateral portion. Degenerative changes in this portion of the acetabulum, the region of the fusion of the ileum and the ischium, are present in all adults, probably as a result of disuse atrophy; it is this area that is often mistakenly regarded as the weight-bearing area of the hip joint. As is discussed in Chapter 1 and at the beginning of this chapter, joints are incongruent, and the incongruence in the hip is at the dome of the acetabulum. C, In the normal hip, the femoral head articulates with the acetabulum with initial contact anteriorly and posteriorly. The roof of the acetabulum probably comes into contact with the femoral head only under certain load conditions (arrow).

FiGURE 10-15—CONT’D  C, Drawing to illustrate the microscopic changes with deep cracks in the cartilage.
common finding in arthritis (Fig. 10-19). Less often, all of the chondrocytes are seen to be necrotic (Fig. 10-20).

Just as the effect of injury to the articular cartilage is reflected by both the matrix and the cells, so, too, is the effect of subsequent cartilage regeneration. Within the pre-existing cartilage matrix, there is focal cell proliferation with clumps, or clones, of chondrocytes (Fig. 10-21) and, when the tissue is stained with toluidine blue, there is often intense metachromasia of the matrix around these clumps of proliferating chondrocytes, evidence of increased PG synthesis. This process can be thought of as intrinsic repair.

In a damaged joint, extrinsic repair by new cartilage may be initiated from either or both of two possible sites: either from the joint margin or from the subchondral bone. Extrinsic repair of cartilage, which develops from the joint margin, can be seen as a hypercellular layer of cartilage extending over, and sometimes dissecting into, the existing cartilage (Fig. 10-22). This extrinsic repair cartilage is usually much more cellular than the pre-existing articular cartilage, and the chondrocytes are evenly distributed throughout the matrix (Figs. 10-23 and 10-24). On microscopic examination of hematoxylin and eosin (H&E) sections, this type of repair cartilage can easily be overlooked. However, examination under polarized light will clearly demonstrate the discontinuity between the collagen network of the repair cartilage and that of the pre-existing cartilage (Fig. 10-25).
In arthritic joints in which loss of the articular cartilage has denuded the underlying bone, and especially in cases of OA, there are frequently small pits in the bone surface, from which protrude small nodules of firm, white tissue. On microscopic examination, these nodules have the appearance of fibrocartilage and arise in the marrow spaces of the subchondral bone (Fig. 10-26). They may

FIGURE 10-20 Photomicrograph to demonstrate total cartilage necrosis. Note also the horizontal cleft resulting from failure of the cartilage matrix to resist shear forces within its substance (H&E, × 10 obj.).

FIGURE 10-21 Photomicrograph of a portion of largely nonviable cartilage demonstrates a large nest of proliferating chondrocytes in the deep zone (H&E, × 10 obj.).

FIGURE 10-22 Gross specimen (A) demonstrates intrinsic cartilage repair, as evidenced by a white, wedge-shaped opaque area between the normal surface and the normal deeper cartilage. Photomicrograph of this area (B) shows proliferating cells, cell clumping, and disarrayed collagen. Under polarized light (C), one can more easily see the disarrayed collagen in the central area of the cartilage (× 4 obj.).
CHAPTER 10 THE DYSFUNCTIONAL JOINT 243

FIGURE 10-23  After cartilage damage, there may be regeneration of both normal cells and matrix. A, The photomicrograph shows residual normal cartilage covered by a thick layer of reparative cartilage. B, When viewed under polarized light, as in this figure, one can appreciate the alteration in the collagen structure of the matrix. The concept of articular cartilage repair is an important consideration in the management of patients with arthritis (H&E, x 10 obj.).

FIGURE 10-24  A, A section through the articular surface of an arthritic joint demonstrates extrinsic reparative fibrocartilage, which extends to the tidemark of the original articular hyaline cartilage (H&E, x 4 obj.). B, The same field photographed with polarized light shows the coarse collagen fibers in the reparative cartilage and the discontinuity of the collagen between the calcified zone and the reparative cartilage above.

FIGURE 10-25  A, Photomicrograph of a section through the articular surface of an arthritic joint demonstrates extensive fibrocartilaginous repair overlying residual hyaline cartilage (H&E, x 4 obj.). B, The same field photographed with polarized light.
Section IV

Arthritis

extend over the previously denuded surface to form a more or less continuous layer of repair tissue (Fig. 10-27). Most cases of OA reveal both intrinsic and extrinsic repair of cartilage (Fig. 10-28).

The chondrocytes themselves are intimately involved in both the breakdown and synthesis of cartilage matrix, and a wide range of growth factors and cytokines are involved in these processes both as part of the regulation of normal matrix and in the processes involved in the repair of osteoarthritic cartilage. The enzymes that break down collagen and PG, the metalloproteinases, are themselves regulated by proinflammatory cytokines such as tumor necrosis factor and interleukin-1. Three main groups of metalloproteinases, the stromelysins, gelatinases, and collagenases, have been identified. The stromelysins degrade the PGs and basement membranes, and the collagenases the fibrillar proteins. It is probably important to realize that while the PGs are broken down and replaced rapidly, replacement of the fibrillar collagen is very slow. (Therefore, it might be useful therapeutically to block collagenase activity in the early stages of the arthritic process.)

Injury and Repair of Subchondral Bone

Arthritis is a disease that affects not only the articular cartilage but also the underlying bone and the structures around the joint.

As the articular cartilage is eroded from the articular surface, the underlying bone is subjected to increasingly localized overloading. In subarticular bone that has been thus denuded, there is proliferation
of osteoblasts and formation of new bone (Fig. 10-29), which occurs both on the surfaces of existing intact trabeculae and around microfractures. In radiographs of arthritic joints, this new bone may appear as increased density or sclerosis.

A further result of increased local stress is that the surface bone is likely to undergo focal pressure necrosis (Fig. 10-30). (This superficial necrosis is different both in its etiology and pathogenesis from that associated with primary subchondral avascular necrosis, which itself leads to secondary OA. However, in clinical practice, differentiation between the two may be difficult, especially in the late stages of primary subchondral avascular necrosis [see Chapter 15].)

Subarticular radiolucencies (cysts) are usually seen only where the overlying cartilage is absent (Fig. 10-31). Such cysts are common in cases of OA and are believed to result from transmission of interarticular pressure through defects in the articulating bony surface into the marrow spaces of the subchondral bone (Fig. 10-32). The cysts increase in size until the pressure within them is equal to the intra-articular pressure. Cysts may also occur because of focal tissue necrosis. [In cases of arthritis due to rheumatoid disease, tuberculosis, gout, or synovial tumors, periarticular radiologic lucencies (cysts), may be associated with erosion of the marginal subchondral bone by the diseased synovium.]

**Osteochondral Loose Bodies**

Separated fragments of bone and cartilage from a damaged joint surface may become incorporated into the synovial membrane and

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**FIGURE 10-28** Microscopic examination of the articular cartilage covering of an osteoarthritic joint, which frequently shows a heterogenous mix of extrinsic reparative cartilage, intensive repair, and residual cartilage as shown in this photomicrograph (H&E, × 10 obj.).

**FIGURE 10-29** Photomicrograph shows increased osteoblastic activity and trabecular thickening underlying an area of cartilage erosion. (Section taken from the edge of a denuded and eburnated area) (H&E, × 10 obj.).

**FIGURE 10-30** A portion of the eburnated surface of an osteoarthritic joint demonstrates focal superficial bone and bone marrow necrosis, which is seen macroscopically as an opaque yellow area.
Intra-articular pressure

Intra-osseous pressure

**FIGURE 10-31** A, An area of cystic degeneration in the subchondral bone of the superior surface of a femoral head. Such cysts are usually seen only in the absence of the overlying articular cartilage. Note also the large, flat osteophyte on the medial surface. B, A radiograph of the specimen. C, Photomicrograph of the subchondral bone cyst shown in A and B. In this case, the cyst was filled with a mucoid fluid and lined by a dense fibrous membrane. However, frequently the lytic area is entirely filled by loose fibrous tissue (H&E, × 2.5 obj.).

digested, or may remain free as loose bodies in the joint cavity (Fig. 10-33). Under certain circumstances, proliferation of cartilage cells occurs on the surface of these loose bodies and consequently they grow larger (Fig. 10-34). As they grow, their centers become necrotic and calcified. In histologic sections, it is possible to visualize periodic extension of this central calcification in the form of concentric rings that increase in number as the loose body grows larger (Fig. 10-35).

**FIGURE 10-32** With the intrusion of synovial fluid into the subchondral bone, the bone becomes resorbed and a cyst is formed, which will increase in size until the intraosseous pressure is equal to the intra-articular pressure.

**FIGURE 10-33** Traumatic arthritis of the elbow. A loose body (left) has formed from the portion of the articular surface that is missing from the radial head (right).
**FIGURE 10-34** Photomicrograph shows the proliferation of immature cellular cartilage on the surface of a cartilaginous loose body; the original cartilage is seen in the lower part of the picture. Through this process of cartilage cell proliferation, loose bodies may grow to an enormous size (H&E, × 4 obj.).

**FIGURE 10-35** A, Low-power photomicrograph of a cartilaginous loose body (H&E, × 1.25 obj.). B, Photomicrograph of a section through a loose body. One can discern the concentric rings of growth. The tissue towards the center of the loose body is calcified (H&E, × 4 obj.). C, Higher power view (H&E, × 25 obj.).
Sometimes the bodies reattach to the synovial membrane, in which case they are invaded by blood vessels. Endochondral ossification then occurs and the loose bodies become bony (Fig. 10-36). Occasionally, in cases of OA, the loose bodies are so numerous that they must be distinguished from those that occur in primary synovial chondromatosis (Fig. 10-37) (see Chapter 21).

There is some degree of loose body formation in many types of arthritis, including inflammatory RA, in which fibrinous loose bodies (rice bodies) may be numerous.

**Ligaments**

Microscopic evidence both of lacerations and of repair by scar tissue is common in the ligamentous and capsular tissue around an arthritic joint. Whether these preceded the arthritic process or whether they are a consequence of it often cannot be determined by microscopic examination; however, there is abundant evidence from clinical studies that severe ligamentous injury is a significant cause of OA, especially in athletes and those engaged in heavy physical labor.

![Figure 10-36](image-url)
Injury of the Synovial Membrane

Even when cases of arthritis that have a primary synovial etiology have been excluded, microscopic examination of the synovium still demonstrates some degree of synovitis.

Injury and breakdown of cartilage and bone result in increased amounts of breakdown product and particulate debris within the joint cavity. This is removed from the synovial fluid by phagocytic cells (the A cells) of the synovial membrane. In consequence, the membrane becomes both hypertrophic and hyperplastic (Figs. 10-38 to 10-40). In addition, the breakdown products of cartilage and bone matrix evoke an inflammatory response.

For this reason, some degree of chronic inflammation can be expected in the synovial membrane of arthritic joints, even when the injury has been purely mechanical. Inflammation is more prominent where there has been rapid breakdown of the articular components, as evidenced by the presence in the synovium of bone and cartilage detritus (Fig. 10-41).

Histologic studies have shown that there may be a similarity between the degree of inflammatory response as seen in some cases of severe OA and that of RA. However, in OA, the synovial inflammation is likely to be the result of cartilage breakdown, whereas in RA, the synovial inflammation is the cause of the cartilage breakdown.
Extension of the hyperplastic synovium onto the articular surface of the joint (i.e., a pannus) is a common finding even in OA, particularly in the hip. However, the extent and the aggressiveness of this pannus with respect to underlying cartilage destruction is much less marked in OA than in RA (Fig. 10-42).

Under normal conditions, the synovial membrane is responsible for the nutrition of articular cartilage. In this regard, it is to be expected that the chronically inflamed and scarred synovial membrane of an arthritic joint functions less effectively than that of a normal joint. Disturbance in synovial nutrient function, as well as increased enzymatic activity, may very well contribute to the chronicity of the arthritic process. The hypertrophied and hyperplastic synovium is also likely to be traumatized as it extends into the joint cavity. Evidence of bleeding into the joint, with subsequent hemosiderin staining of the synovial membrane, is a common histologic finding and may occasionally be marked. When this is the case, and despite their similar color, the

**FIGURE 10-41**  
A, In association with rapid destruction of a joint, the synovium often shows a marked hyperplasia and chronic inflammation with pieces of detached bone and cartilage embedded within it, as seen here (H&E, × 4 obj.). B, In a higher power view, fragments of bone and cartilage, as well as foci of histiocytes and phagocytic giant cells, are present (H&E, × 10 obj.).

**FIGURE 10-42**  
A, Fibrous pannus extending over the surface of the damaged articular cartilage in a patient with osteoarthritis (H&E, × 1 obj.). B, Higher power view of A (H&E, × 10 obj.).
orange-brown staining of the fine villous synovium seen at operation should not be confused with the swollen papillary synovium of pigmented villonodular synovitis (Fig. 10-43).

**Synovial Fluid in an Injured Joint**

Normal synovial fluid, a dialysate of plasma to which hyaluronic acid produced by the B cells of the synovial lining is added, is viscous, pale yellow, and clear. Even in large joints the volume is small.

Examination of synovial fluid is extremely helpful in the diagnosis of arthritis for determining both the cause and the stage of the disease. Whatever the cause of arthritis, the synovial fluid is altered (Fig. 10-44, and Tables 10-1 and 10-2). (For a discussion of the examination of synovial fluid for crystals, see Chapter 12.) In cases of inflammatory arthritis, there is an increased volume of synovial fluid, whereas the amount of hyaluronic acid is markedly diminished. This leads to a typical decrease in viscosity. However, in post-traumatic forms of osteoarthritis, the amount of hyaluronic acid is increased, resulting in an extremely viscous fluid. Often there is also an increase in volume, although not to the same degree as that which is seen in the inflammatory arthritides.

**TABLE 10-1** Normal Synovial Fluid

<table>
<thead>
<tr>
<th>Physical Data</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount in knee (milliliters)</td>
<td>1.1</td>
<td>0.13–3.5</td>
</tr>
<tr>
<td>Specific gravity (20° C)</td>
<td></td>
<td>1.0081–1.015</td>
</tr>
<tr>
<td>Viscosity (37° C) relative to water</td>
<td>235</td>
<td>5.7–1160</td>
</tr>
<tr>
<td>Cell count per mm³</td>
<td>63</td>
<td>13–180</td>
</tr>
<tr>
<td>Differential %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>24.6</td>
<td>0–78</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes</td>
<td>6.5</td>
<td>0–25</td>
</tr>
<tr>
<td>Monocytes</td>
<td>47.9</td>
<td>0–71</td>
</tr>
<tr>
<td>Macrophages</td>
<td>10.1</td>
<td>0–26</td>
</tr>
<tr>
<td>Synovial lining cells</td>
<td>4.3</td>
<td>0–12</td>
</tr>
<tr>
<td>pH</td>
<td>7.434</td>
<td>7.31–7.74</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 10-1 Normal Synovial Fluid—cont’d

<table>
<thead>
<tr>
<th>Physical Data</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inorganic Substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes (Na, K, Cl, CO\textsubscript{3})</td>
<td>Approximately the same as plasma</td>
<td></td>
</tr>
<tr>
<td>Calcium, phosphate, sulfate</td>
<td>Approximately the same as plasma</td>
<td></td>
</tr>
<tr>
<td><strong>Organic Substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaluronic acid (mg/mL)</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Nonprotein nitrogen</td>
<td></td>
<td>Approximately the same as plasma</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lipid (mg/mL)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Mucin nitrogen (mg/mL)</td>
<td>1.04</td>
<td>0.68–1.35</td>
</tr>
<tr>
<td>Mucin glucosamine (mg/mL)</td>
<td>0.74</td>
<td>0.12–1.32</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td>Approximately the same as plasma</td>
</tr>
</tbody>
</table>


### TABLE 10-2 Examination of Synovial Fluid

<table>
<thead>
<tr>
<th></th>
<th>Normal Synovial Fluid</th>
<th>Noninflammatory</th>
<th>Synovial Fluid with Disease</th>
<th>Septic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical example</td>
<td></td>
<td></td>
<td>Osteoarthritis</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Cartilage debris</td>
<td>0</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (mL knee)</td>
<td>&lt;3.5</td>
<td>&gt;3.5</td>
<td>&gt;3.5</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td>Clear</td>
<td>Clear yellow</td>
<td>Opalescent yellow</td>
<td>Turbid yellow to green</td>
</tr>
<tr>
<td>Viscosity</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>WBCs per mm\textsuperscript{3}</td>
<td>200</td>
<td>200–2000</td>
<td>2000–100,000</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes (%)</td>
<td>&lt;25</td>
<td>&lt;25</td>
<td>50% or more</td>
<td>90% or more</td>
</tr>
<tr>
<td>Culture</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Mucin clot</td>
<td>Firm</td>
<td>Firm</td>
<td>Friable</td>
<td>Friable</td>
</tr>
<tr>
<td>Fibrin clot</td>
<td>None</td>
<td>Small</td>
<td>Large</td>
<td>Large</td>
</tr>
<tr>
<td>Glucose (% blood glucose)</td>
<td>50–100</td>
<td>50–100</td>
<td>20–75</td>
<td>1–5</td>
</tr>
<tr>
<td>Total protein</td>
<td>Equal to normal joint</td>
<td>Elevated</td>
<td>Elevated</td>
<td></td>
</tr>
</tbody>
</table>

WBCs, white blood cells.

The Noninflammatory Arthritides

Archibald Edward Garrod (November 1857—March 1936). The fourth son of Sir Alfred Baring Garrod, who discovered the abnormal uric acid metabolism associated with gout. Garrod was a proponent of scientific research as the foundation of medical practice, and published "A Treatise on Rheumatism and Rheumatoid Arthritis" (1890). He helped found the Quarterly Journal of Medicine to provide a forum for more fundamental research into the processes of disease. He published "The Incidence of Alkaptonuria: A Study in Chemical Individuality" in 1902, and he introduced the terms Rheumatoid Arthritis and Osteoarthritis. He succeeded William Osler as Regius Professor of Medicine at Oxford. (From Hopkins FG: Archibald Edward Garrod. Obituary Notices of Fellows of the Royal Society, vol 2, 1936-1938, pp. 225-228. From the Wellcome Library, London.)

Eric Bywaters (June 1910—April 2003). An interest in biology developed at school led Bywaters to a career in medicine. He qualified at the Middlesex Hospital Medical School in the University of London with a gold medal and honors in pathology. He then spent 2 years of his graduate education at the Massachusetts General Hospital at the invitation of Walter Bauer, a pioneer in rheumatology in the United States. As a clinician, his forte was his expertise in pathology, which helped to clear up many ambiguities of diagnosis. (From Dixon A: Eric Bywaters 1910-2003. Rheumatology 2003;42:1025-1027. Reprinted by permission of Oxford University Press.)

### Chapter 11

<table>
<thead>
<tr>
<th><strong>Osteoarthritis (Degenerative Joint Disease)</strong></th>
<th><strong>254</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Considerations</strong></td>
<td><strong>254</strong></td>
</tr>
<tr>
<td><strong>Pathologic Findings</strong></td>
<td><strong>254</strong></td>
</tr>
<tr>
<td><strong>Natural History</strong></td>
<td><strong>261</strong></td>
</tr>
<tr>
<td><strong>Ochronosis (Alkaptonuria)</strong></td>
<td><strong>265</strong></td>
</tr>
<tr>
<td><strong>Arthritis Secondary to Subchondral Insufficiency Fracture</strong></td>
<td><strong>266</strong></td>
</tr>
<tr>
<td><strong>Rapidly Destructive Osteoarthritis</strong></td>
<td><strong>269</strong></td>
</tr>
<tr>
<td><strong>Osteochondritis Dissecans</strong></td>
<td><strong>273</strong></td>
</tr>
<tr>
<td><strong>Slipped Capital Femoral Epiphysis (Adolescent Coxa Vara)</strong></td>
<td><strong>274</strong></td>
</tr>
<tr>
<td><strong>Congenital Dislocation of the Hip</strong></td>
<td><strong>275</strong></td>
</tr>
</tbody>
</table>
By the use of the term noninflammatory in the title of this chapter, we intend to convey the idea that this type of arthritis, rather than being the result either of infection by any organism or the result of an inflammatory response to an as yet unknown antigen, such as is the case in rheumatoid arthritis (RA), has as its cause a previous mechanical injury or structural alteration.

We have seen in the previous chapter that commonly arthritis may result either from a sudden or gradual change in the geometry of a joint surface; sudden, as with a fracture, or gradual, as in Paget’s disease (one joint) or acromegaly (many joints). Traumatic injury, resulting in a torn ligament in the knee, a torn capsule in the shoulder, or a labral tear and detachment in the hip, may also lead to severe arthritis in the affected joint. Many, if not most, cases of so-called primary idiopathic osteoarthritis (OA) may be explained on these bases.

All injury from whatever cause, as long as it is not fatal, results in a secondary inflammatory response and that response is necessary to the restoration of the status quo, but inflammation is not the cause of OA even though it does affect the course of the disease process. The noninflammatory arthritides are certainly the most commonly encountered form of arthritis in the Western world, and OA in its many and varied presentations is the most commonly encountered condition in orthopaedic practice and often associated with advancing age and obesity.

It is estimated that the disease clinically affects approximately 20 million patients in North America and a similar number in Europe. It clinically presents in three major forms:

- Nodal OA results in Heberden and Bouchard nodes in the small joints of the hands. In contrast to RA, it does not cause significant loss of hand function.
- Axial OA involves mainly the neck and the low back, and the condition is discussed in more detail in Chapter 13.
- OA in weight-bearing joints—the principal topic of this chapter.

**Osteoarthritis (Degenerative Joint Disease)**

**CLINICAL CONSIDERATIONS**

Because in most cases the etiology of OA cannot be determined, there is no generally accepted definition of the disease; however, for the purpose of this discussion the following is offered: ‘Osteoarthritis is a functional disorder of joints characterized by altered joint anatomy, especially by the loss of articular cartilage and the formation of osteophytes. Unlike many other forms of arthritis, it is essentially noninflammatory.’

Four patterns of disease are generally recognized:

1. OA presenting as disease limited to a single large joint, usually the knee or the hip, sometimes with bilateral involvement (Fig. 11-1).
2. A generalized process involving the distal and proximal interphalangeal joints of the hand, the first carpometacarpal joint, and metatarsophalangeal joints (Fig. 11-2).
3. Extreme cases of OA known as Charcot’s joints generally seen in association with a neurologic deficit. In these patients, a characteristic rapidly destructive OA is observed, complicated by the production of multiple loose bodies, severe subluxation, and even dislocation of the joint (Figs. 11-3 to 11-5). The underlying neurologic disorder associated with Charcot’s joint may be a peripheral neuropathy associated with pernicious anemia or diabetes mellitus, or spinal cord degeneration as in tabes dorsalis or syringomyelia.
4. A rare pattern, described clinically, is an erosive OA that radiographically has the features of an inflammatory process. This form of disease usually affects the distal or proximal interphalangeal joints of the hand (Fig. 11-6) but may occasionally involve large joints (Fig. 11-7).

A patient with OA typically presents with reports of pain and usually of stiffness. On examination, movement of the affected joint may be limited and the patient often lacks the capability for full flexion or extension.

The most characteristic radiologic finding is loss of the joint space. In the majority of cases, bony osteophytes are seen around the periphery of the joint, the bone on both sides of the joint exhibits increased density, and cystic lesions can frequently be noted in the subchondral bone especially in the hip.

**PATHOLOGIC FINDINGS**

The most obvious morphologic features of an osteoarthritic joint removed either at surgery or autopsy are damaged cartilage, subarticular cysts, alterations in the shape of the articular surfaces and peripheral bone, and cartilaginous outgrowth (osteophytes). In the presumed...
load-bearing areas of the joint, the cartilage may be entirely absent, and the exposed subchondral bone may have a dense polished appearance like that of marble (eburnation); when this portion of the joint is sectioned, the exposed bone is usually found to be markedly thickened (sclerotic) (Fig. 11-8). As already noted in Chapter 10, the superficial bone in the eburnated areas may be necrotic (see Fig. 10-30).

Adjacent to the surface denuded of cartilage and particularly in the hip joint, cystic defects filled with loose fibromyxoid tissue (or sometimes with a thick mucoid fluid) may be found (Fig. 11-9).

In areas of the joint that do not bear weight, and around its margins, bony and cartilaginous overgrowths (osteophytes or exostoses) develop. The location of the osteophytes in different joints is usually characteristic. In the distal interphalangeal joints, the osteophytes (Heberden’s nodes) are prominent on the dorsal and palmar aspects of both articulating surfaces. In the metatarsophalangeal joint of the
Figure 11-6 Radiograph of the hand of a 45-year-old woman with erosive osteoarthritis, showing the typical involvement of the proximal and distal interphalangeal joints.

Figure 11-7 Radiograph of the hip of a 55-year-old woman with recent complaints of pain and stiffness, showing concentric narrowing of the joint space and erosive changes in both the femoral head and acetabulum. Testing for rheumatoid factor was negative in this case, which was clinically diagnosed as erosive osteoarthritis.

Figure 11-8 A, Photograph of the femoral head removed from a patient with osteoarthritis. Note the absence of the articular cartilage on the superior and lateral aspect of the femoral head and the polished appearance of the exposed bone (eburnation). The remaining surrounding cartilage has a somewhat yellow color and a roughened surface. B, In section, the bone beneath the eburnated surface is much denser. C, Microscopically, the dense bone has an almost cortical appearance. Note the smoothness of the eburnated surface (H&E, partially polarized × 4 obj.).
big toe, the osteophyte is on the medial joint margin (hallux valgus) (Fig. 11-10). In the hip joint, although osteophytes are usually present around the entire joint margin, there is characteristically a large flat osteophyte on the medial articular surface extending to the fovea, and this is associated with lateral subluxation of the femoral head in the acetabulum, which can be seen on the radiographs (Fig. 11-11). Despite the loss of bone and cartilage in some parts of the joint, which is assumed to be the result of overloading and mechanical abrasion, the net effect of the reparative new bone and osteophyte formation is an overall increase in joint size so that in general, an osteoarthritic joint is larger than its normal counterpart (see Fig. 10-12).

**Osteophytes**

Osteophytes form through the process of endochondral ossification in one of two ways. The first involves vascular penetration into existing cartilage. In these areas, the cartilage overlying the bone overgrowth is usually hypercellular, and the process histologically resembles the epiphyseal growth plate in a growing individual (Fig. 11-12). At the base of the osteophyte, there are often remnants of the original tidemark and zone of calcified cartilage. In some cases, these remnants are themselves undergoing ossification, not only from the region of the original subchondral bone but also from the osteophyte itself (Fig. 11-13). Osteophytes may also form from foci of cartilaginous metaplasia at the joint margins. (These foci of cartilaginous metaplasia often occur at the capsular and ligamentous insertions and may be the result of traction injuries [Fig. 11-14].)

In areas of residual cartilage on the articular surface of a diseased joint, there is often marked duplication and irregularity of the tidemark (Fig. 11-15). Evidence of increased endochondral ossification, which expands the periphery of subchondral bone without actually forming an osteophyte, is recognized by irregularity of the bone cartilage junction, increased vascular penetration of the calcified cartilage, and the finding of woven (immature) bone at the bone-cartilage interface, indicating a rapid rate of bone formation at this site (Figs. 11-16 and 11-17).
FIGURE 11-12 Photomicrograph of a section through a marginal osteophyte shows a wedge of bone formation dissecting into the cartilage. The cartilage on the superior articular side of the osteophyte is cellular, and there is more active endochondral ossification on this surface than on the lower surface that faces the subarticular bone (H&E, × 4 obj.).

FIGURE 11-13 A, Photomicrograph showing the edge of an osteophyte with calcification of the reparative tissue above the residual articular cartilage. Note the vascularization of the mineralized matrix (H&E, × 4 obj.). B, Higher power photomicrograph of a portion of articular cartilage trapped under an osteophyte (H&E, × 25 obj.).

FIGURE 11-14 Specimen radiograph to demonstrate the various osteophytes that form around an osteoarthritic femoral head. Note especially the osteophyte on the medial neck of the femur, which results from traction on the medial periosteum following lateral subluxation of the femoral head. Note also the perifoveal osteophytes and the large subarticular cysts.
FIGURE 11-15 Photomicrograph of a portion of the articular cartilage in a patient with osteoarthritis, showing irregularity and duplication of the tidemark. The articular cartilage is relatively intact; however, there are degenerative changes in the superficial chondrocytes (H&E, × 4 obj.).

FIGURE 11-16 A, A radiograph demonstrates the formation of the medial osteophyte, a characteristic finding in osteoarthritis of the hip. Note especially the hair-on-end appearance of the new bone lying on top of the subchondral plate of bone. B, Photograph of the macerated specimen shown in A, which demonstrates the new bone of the osteophyte in three dimensions. C, These tongues of new bone are formed as the result of vascular canals breaking through the calcified articular cartilage and the tidemark (H&E, × 10 obj.).

FIGURE 11-17 Photomicrograph taken with polarized light shows woven bone formation in the subchondral region. This is an indication of accelerated modeling in this region in osteoarthritis (× 25 obj.).
Cartilage

Microscopic examination of the cartilage that remains on the joint surface may reveal many clefts in its substance, most, but by no means all, of which are vertically oriented (Fig. 11-18). The chondrocytes far from the areas of eburnation may show considerable cell replication, with formation of prominent cell nests (Fig. 11-19). However, cell replication does not usually occur adjacent to the eburnated areas (Fig. 11-20). Proteoglycan (PG) staining of the matrix is usually diminished, although, as discussed in the previous chapter, there is evidence from radioactive SO₄ uptake studies that the amount of PG produced by the chondrocytes in OA may be increased, suggesting increased turnover with loss of glycoprotein residues into the synovial fluid.

**FIGURE 11-18** A, Section through the articular cartilage of the patella demonstrates a failure in the matrix with horizontal cleft formation in a patient with chondromalacia patellae. In patients with this condition, a soft blister on the articular surface generally indicates a structural shear failure within the substance of the cartilage (H&E, × 1.25 obj.). B, A high-power view of the cleft shows marked cellular proliferation in the inferior cartilage as opposed to the cartilage on the side of the cleft closest to the surface (H&E, × 10 obj.).

**FIGURE 11-19** Photomicrograph of fibrillated cartilage away from the eburnated area shows a considerable proliferation of chondrocytes within the cartilage matrix. Many of the chondrocytes are seen to form cell nests or clones (H&E, × 10 obj.).

**FIGURE 11-20** Low-power photomicrograph of the articular surface adjacent to an eburnated area. The articular cartilage contains vertical clefts resulting from fraying and splitting of the collagen fibers at the surface of the cartilage but, in contrast to Figure 11-19, no obvious chondrocyte replication (H&E, × 10 obj.).
Synovial Membrane
The synovial membrane may show villous proliferation, slight hyperplasia of the lining cells, and mild chronic inflammation (Figs. 11-21 and 11-22). Small osteochondral loose bodies are commonly found in the synovium and in the joint cavity. In some cases of degenerative arthritis of the knee (and occasionally in rheumatoid arthritis), a cystic herniation of the synovium may occur into the popliteal space, commonly referred to as Baker’s cyst (Fig. 11-23).

NATURAL HISTORY
A number of questions may be asked about OA, including:
- Is it a single disorder or a family of disorders?
- What is the role of acute and chronic trauma in its pathogenesis?
- Is OA an inevitable consequence of aging?
- How do the anatomic, physiologic, biochemical, and mechanical alterations in cartilage matrix interrelate in the pathogenesis of OA?
- What roles do the extracartilaginous tissues and structures of the joint play in OA?
- Under what circumstances does inflammation develop and what is its role in OA?
- Does articular cartilage undergo repair in OA, and is there repair of the joint as a functional mechanism?

Some of the answers to these questions have been addressed in the preceding chapter.
In about one fifth of the patients, it is evident to the clinician that an antecedent condition, such as congenital hip dysplasia or Paget’s disease, is causally related to the OA, which can therefore be considered secondary OA (Box 11-1). Individuals affected by secondary OA are likely to be younger than those with primary (idiopathic) OA, who are usually older than 60 years of age.

It is obvious that OA is not necessarily the consequence of aging per se, because in most people, most joints remain essentially normal even into extreme old age.

A number of autopsy studies have demonstrated the incidence of degenerative changes in various joints, as well as its progression from mild to severe disease. As might be expected the incidence at autopsy is much more than the clinical incidence of disease (Table 11-1).

![Figure 11-21 A](image1.png) The synovium from a patient with osteoarthritis exhibits a marked villous pattern. The villi are fine and delicate, an appearance that grossly reflects the lack of any significant cell infiltrate in the subsynovium. B, Photomicrograph of the specimen demonstrates the overgrowth of the synovial lining cells without significant inflammatory cell infiltration in the subsynovial tissue (H&E, × 4 obj.).

![Figure 11-22 A](image2.png) Photomicrograph of the synovial membrane in a patient with osteoarthritis (OA). The villous pattern of the synovium and hyperplasia of the synovial lining cells are evident. In this patient, as in many patients with OA, one may also note a mild chronic inflammatory infiltrate in the synovial tissue. B, This inflammation can rarely be severe as seen here, where there is also an included cartilage fragment (both images, H&E, × 25 obj.).
The pathogenesis of OA can be understood only in terms of the interdependence of anatomy, physiology, biochemistry, and mechanical function. All components of the joint play a role in the pathogenesis of the disease, not just cartilage. Tissue breakdown always results in an inflammatory response, which also plays its role in the disease processes.

**Radiographic Staging**

The availability of a large volume of tissue specimens from hip replacement arthroplasty, together with the availability of these patients’ clinical radiographs and case histories, has made it possible for us to gain further insights into the natural history of OA of the hip. One of the problems with most classifications of the radiographic changes in OA is that they tend to miss the dynamic progressive nature of the disease, which as already discussed, involves mechanical wear, cell injury, and repair. It has been possible for us to stage the disease radiographically not only on the basis of horizontal comparisons of radiographs in different patient’s hips but also in longitudinal studies of serial radiographs of the same patient. Our observations lead us to suggest that there are three stages in the disease process that can be appreciated radiographically:

- **Stage I** is characterized by narrowing or absence of the joint space, with preservation of the subchondral bone contours of the femoral head and of the acetabulum. In this early stage of the disease, migration of the femoral head has not occurred beyond the distance caused by the loss of the cartilage (Fig. 11-24).

- **Stage II** is characterized by complete absence of the superior joint space, with incomplete or complete loss of the subchondral bone contour. In this stage bone loss may be marked, and subchondral sclerosis and cystic changes in the bone on both sides of the joint are prominent. Migration of the joint, in most cases superiorly and laterally, also occurs relative to the bone loss (Fig. 11-25).

- **Stage III** is characterized by some reappearance of the joint space after maximal bone loss and migration have occurred. The bone contours again become relatively well defined. Sclerosis has diminished, and cysts have become indistinct (Fig. 11-26).

This radiologic staging corresponds well historically to the duration of symptoms.

**TABLE 11-1 Incidence of Cartilage Changes and Osteoarthritis at Autopsy in Joints at Different Ages**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Knee</th>
<th>Shoulder</th>
<th>Hip</th>
<th>Elbow</th>
<th>Great Toe</th>
<th>Acromioclavicular</th>
<th>Sternoclavicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
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<tr>
<td>15–19</td>
<td>3.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>20–29</td>
<td>9.2</td>
<td>0.0</td>
<td>0.8</td>
<td>0.0</td>
<td>0.8</td>
<td>0.0</td>
<td>1.7</td>
</tr>
<tr>
<td>30–39</td>
<td>48.1</td>
<td>1.0</td>
<td>2.0</td>
<td>0.0</td>
<td>7.8</td>
<td>0.0</td>
<td>18.0</td>
</tr>
<tr>
<td>40–49</td>
<td>74.0</td>
<td>0.8</td>
<td>4.7</td>
<td>0.0</td>
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<td>26.9</td>
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<td>50–59</td>
<td>87.1</td>
<td>2.6</td>
<td>14.3</td>
<td>0.7</td>
<td>44.8</td>
<td>0.7</td>
<td>61.7</td>
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<tr>
<td>60–69</td>
<td>92.6</td>
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<td>15.7</td>
<td>89.4</td>
<td>16.7</td>
<td>95.8</td>
</tr>
</tbody>
</table>

Columns A: Joints showing naked eye evidence of cartilage destruction to a lesser or greater degree.
Columns B: Joints showing naked eye evidence of moderate to severe osteoarthritis.

A number of correlations can be made between this system of radiographic staging and the pathologic appearance of the resected specimens. The most striking of these correlations is that reparative cartilage is much more prominent in radiographic stage III than in stage I (Figs. 11-27 to 11-30). Subchondral cysts are most prevalent in stage II and tend to decrease in number in stage III.

When considering the processes of injury and repair within cartilage, bone, and synovium that make up the joint, it is important not to lose sight of the fact that joint function depends on the anatomy of the entire structure. If the repair processes observed in the various tissues are not directed toward restoration of the shape of the joint as well as restoration of stability and of an equitable loading pattern, then they serve no useful purpose.

The most easily recognized evidence of the attempt at functional restoration is the production of new bone, in the form of osteophytes, at various sites along the joint surface, particularly at the joint margins. Such remodeling of bone occurs early in the process of OA. The degree of remodeling by this process can be considerable, and its efficacy is reflected clinically. The presence of osteophytes in the knee and hip by no means always heralds the development of symptomatic OA. Radiographic studies have shown that two thirds of knees that exhibit evidence of osteophyte formation, even when followed up for as long as 17 years, do not develop other degenerative changes.

Discussion

The term OA was first introduced by Archibald E. Garrod, in the 1890s. In 1909, Nichols and Richardson, on the basis of anatomic features, distinguished the two major categories of chronic arthritis by separating inflammatory arthritis from degenerative arthritis: “These (various) joint lesions can be divided with great definiteness into two pathological groups: (1) those which arise from primary proliferative changes in the joints, chiefly in the synovial membrane and perichondrium, and (2) those which arise primarily as a degeneration of the joint cartilage. These two pathological groups are characterized by distinct gross and histological differences.” Nichols and Richardson went on to state that “the earliest change to be observed in hypertrophic arthritis (OA) is a roughening of the cartilage, which begins near the center of the articular surface, i.e. at the point where pressure and friction between the ends of the bones is greatest.”
FIGURE 11-27 The radiograph shown in B was taken 8 years after that in A. It demonstrates the improvement that may occur in the radiographic appearance of a patient with osteoarthritis, even without treatment.

FIGURE 11-28 Gross superior view of a femoral head from a patient with radiographic stage I osteoarthritis shows an area of complete cartilage loss, with polishing or eburnation of the underlying bone.

FIGURE 11-29 In this gross specimen of a deformed femoral head from a patient with radiologic stage III osteoarthritis, the weight-bearing superior surface has been recovered with an irregular, cobble-stoned layer of cartilage.

FIGURE 11-30 The radiographic and to some extent the clinical signs of arthritis depend on the balance between injury to the joint and repair of the joint (left). Deterioration is taking place because breakdown (i.e., loss of cartilage, bone, and bone shape, as well as bone necrosis) is proceeding more rapidly than repair (i.e., regeneration of cartilage and formation of new bone) (center). Both injury and repair are proceeding at about the same pace and the joint is stabilized (right). Repair is proceeding more rapidly than injury, leading to morphologic and perhaps clinical improvement.
Since the time of that report, most authors on the subject have concluded that the earliest changes in OA are found in ‘those areas in which weight bearing is pre-eminently concentrated, and which are the most severely subjected to shearing and twisting types of stress.’

The wear-and-tear theory of causation, to which this author does not subscribe, has had a stultifying effect on medical opinion with regard to its views on prevention and treatment of the disease. My belief is that it is more helpful to regard clinical arthritis as the consequence of a breakdown of normal physiologic pathways. Thus the etiology of arthritis can be defined, in general terms, as any condition that changes the shape of the articulating surface, changes the joint support, or alters the tissue matrices. It is not an inevitable disease resulting from wearing out of the joint by long use. Rather, OA is a disease of multiple etiologies, and searches for a single, all-encompassing cause are fruitless. Although dysfunction may begin in any of the structures that make up the joint, by the time the disease comes to the attention of a clinician, most structures of the joint are involved. Because of this overall involvement, it is often impossible, especially in the later stages of disease, for the pathologist to determine the etiology.

**Ochronosis (Alkaptonuria)**

Ochronosis was first described by Virchow to denote a brownish black pigmentation of connective tissue in patients with alkaptonuria. Generalized degenerative joint disease or OA is often the presenting disease in ochronosis. The condition results from a rare autosomal recessive hereditary disorder of tyrosine and phenylalanine degradation, in which the absence of the enzyme homogentisic acid oxidase leads to the accumulation of homogentisic acid in the body. The defect has been mapped to the *HGD* gene on arm 3q. The presence of excess homogentisic acid in the urine causes the condition known as alkaptonuria, characterized by darkening of the urine on exposure to air (this discoloration may be the only abnormality in children affected by ochronosis) (Fig. 11-31). However, in time, the widespread deposition of dark oxidative products occurs in virtually all collagen-containing structures in the body, including the sclerae and the skin. The predominant deposition of homogentisic acid in cartilage (including the intervertebral discs and articular cartilage) causes collagen brittleness and consequent breakdown of the tissue, which, in turn, leads to spondylosis and arthropathy, in which the large joints are most severely involved (Fig. 11-32).

Radiographic examination of the spine of patients with ochronosis reveals calcification of the intervertebral discs, with narrowing of the disc spaces (Fig. 11-33). The changes seen in the large diarthrodial joints may be indistinguishable on radiographs from OA with osteophytosis and subchondral bone sclerosis (Fig. 11-34).

Gross examination of the affected tissues reveals a brownish black discoloration, often with degenerative changes (Fig. 11-35). Histologic features of ochronosis include the intracellular accumulation of pigment and irregular fragments of pigmented cartilage that may be embedded in the synovium, a phenomenon that suggests a rapidly destructive arthropathy similar to that seen in a Charcot joint (Fig. 11-36). Ultrastructural study of the affected tissue has shown widening and fragmentation of collagen fibers in association with the deposition of the pigment in the matrix (Fig. 11-37).

The precise mechanism of the tissue injury is not fully understood, but the disruption of collagen cross-linking by metabolites of homogentisic acid is a probable explanation.

**FIGURE 11-31** In the flask on the left is urine from a patient with ochronosis, which has been allowed to stand for 15 minutes. Some darkening, due to oxidation of homogentisic acid, is apparent at the surface. After 2 hours, with shaking, the specimen is entirely black (flask on the right).

**FIGURE 11-32** Section obtained at necropsy through the spine of a patient with ochronosis. Note the black discoloration of the intervertebral discs and the pronounced narrowing and irregularity of the disc spaces.
Arthritis Secondary to Subchondral Insufficiency Fracture

Hip fractures are an increasingly important public health problem in the elderly. It has been estimated that in the United States, more than 500,000 cases annually will occur by the year 2030. These estimates underscore the importance of preventive measures to delay the onset of osteoporosis. The most commonly encountered fractures are through the femoral neck, either subcapital, intertrochanteric, or subtrochanteric. Stress fractures of the femoral neck, although much less common, are also well recognized. Until recently, immediately subarticular (subchondral) fracture has been most commonly observed as a secondary phenomenon in patients with primary osteonecrosis of the femoral head.
Recent clinical reports of primary subarticular fractures of the femoral head include stress osteopathy in young military trainees, insufficiency fracture in renal transplant recipients, and most commonly in our experience elderly osteoporotic women. These reports have stressed the importance of its differentiation from osteonecrosis, especially when using magnetic resonance imaging (MRI), because the initial diagnosis will affect the treatment and management of the patient. Many of the clinically reported cases have resolved after conservative therapy without progressing to collapse or surgery. However, in our experience histologic evidence of subchondral fracture as the etiology of acute onset hip pain in elderly woman has become increasingly commonplace, and in a recent study accounted for 5.1% of all total hip replacement in our institution.

Clinically, patients with subchondral insufficiency fracture (SIF) are mostly elderly women who are osteopenic and overweight. These features distinguish this patient population from the majority of those with osteonecrosis. In the published cases of insufficiency fracture, shortly after the onset of acute hip pain, radiographic changes were reported to be unremarkable (which would seem inappropriate to the reported severity of pain in these patients) (Fig. 11-38). However, MRI has shown a bone marrow edema pattern, which in about half the cases is associated with a focal low-intensity band on T1 (Fig. 11-39). Although a low-intensity band is also observed in primary osteonecrosis, it generally differs in two ways. First, in osteonecrosis, the subchondral bone segment proximal to the low-intensity bands...
Section IV Arthritis

Arthritis does not show high-intensity on fat suppression, whereas in subchondral fracture, it usually does. Second, the shape of the low-intensity band in osteonecrosis is usually concave to the articular surface. In subchondral fracture, the low-intensity band on T1 may often parallel the articular surface and show a serpiginous shape (however, in our experience there is considerable variation, which may make the differentiation by MRI difficult).

A femoral head removed in the early stages of an insufficiency fracture is grossly unremarkable except for focal subchondral hemorrhage, which may be very difficult to find (Fig. 11-40).

Histopathologically the most characteristic finding in the cases reported was the presence of fracture callus and granulation tissue along both edges of the fracture line (Fig. 11-41). Such cases had been previously diagnosed histopathologically as osteonecrosis, presumably because of the small foci of necrosis caused by the fracture (Fig. 11-42). (Most important, failure to recognize the true etiology initially was most likely because the concept of primary SIF was unknown to us.) However, we are now convinced that small foci of necrosis seen only around an area of fracture should not be considered as sufficient evidence for a diagnosis of primary osteonecrosis. (Because subchondral fracture of the femoral head is a common complication in cases of osteonecrosis, generally believed to be the cause of the symptoms, a patient with a painful hip shown by imaging studies to have a subchondral fracture has been generally assumed to have osteonecrosis.)

The signs and symptoms of both fracture secondary to osteonecrosis and insufficiency fracture are similar. However, although most patients with osteonecrosis are in their early 40s, most insufficiency fractures are seen in patients older than 60 years of age who are radiologically osteoporotic.

Spontaneous osteonecrosis of the knee has been recognized as a distinct form of osteonecrosis since it was first described in 1968. The lesion is clinically characterized by the sudden onset of severe knee joint pain in older patients and is not usually associated with systemic disorders or previous corticosteroid therapy. In general, the lesion is immediately subarticular and is located in the medial femoral condyle. In the early period after the onset of pain, the radiographic findings are usually unremarkable (Fig. 11-43).

FIGURE 11-40 A, Because of the unremitting pain, a total joint replacement was done on the patient shown in Figures 11-38 and 11-39, but except for mild marginal osteophytes, no abnormality of the articular cartilage was seen. B, Section taken through the femoral head showed no discernible abnormalities and in particular no evidence of osteonecrosis. C, A radiograph of one of the slices shows subtle alterations in the architecture of the subchondral bone that were not immediately obvious to the prossector. D, A microscopic section of the slice in C. Slight thickening is focally present in the subchondral region (H&E, × 1 obj.).
In our experience, spontaneous osteonecrosis of the knee (SPONK) is less common and has a very different morphology than classic osteonecrosis of the knee. The classic nontraumatic form of osteonecrosis of the knee has been associated with various factors, especially corticosteroid intake in patients with RA or lupus erythematosus. It is often bilateral, frequently involves large portions of the epiphysis and metaphysis, and usually is apparent on plain radiographs at the time of the onset of symptoms.

We now believe that the histopathologic findings support the view that subchondral insufficiency fracture resulting from underlying osteoporosis is the etiology of so-called spontaneous osteonecrosis of the knee.

Rapidly Destructive Osteoarthritis

First reported in the literature by Postel and Kerboull in 1970, rapidly destructive arthrosis (RDA) of the hip joint is a relatively uncommon form of arthritis that is seen mostly in elderly women. RDA is characterized by rapid joint destruction within 6 to 12 months and usually less. Disappearance of the joint space is the typical initial finding on radiographs, followed by rapid disappearance of the femoral head. In general, proliferative changes are minimal. The majority of cases are unilateral, without evidence of antecedent OA, osteonecrosis, neuropathy, infection, or inflammatory disease (Fig. 11-44).

Since we became aware of SIF, we have come to realize that this condition is relatively common in the elderly population, and that some cases of SIF show rapid disappearance of the hip joint space.
In most cases of RDA, we believe there is often evidence of subchondral fracture histologically (Fig. 11-45). The articular cartilage at the superior portion of the femoral head may be thinned, detached from the subchondral bone or lost. In the superficial portion of the marrow space, round-to-oval foci of granulomatous tissue are usually observed, in which small fragments of bone and articular cartilage embedded in amorphous eosinophilic debris are found surrounded by aggregated epithelioid histiocytes and giant cells (Fig. 11-46). This type of granulomatous lesion has been observed to be prominent in the advanced stages of RDA, and we consider it pathognomonic of rapid joint destruction. No evidence of primary osteonecrosis was observed in these specimens.

FIGURE 11-43 A, Anteroposterior radiograph of the knee in a 58-year-old woman who reported sudden onset of pain in the knee. Irregularity of the articular surface of the medial femoral condyle is evident. B, Lateral view of the same knee shown in A reveals an extensive subchondral fracture of a portion of the articular surface of the femoral condyle. C, Photograph of the resected medial femoral condyle shows fracturing of the articular cartilage around the infarcted area. D, Frontal slice taken through the medial condyle. The zone of bone necrosis lies immediately under the articular surface and is characterized by an opaque yellow appearance. Immediately beyond the necrotic zone is a band of hyperemia. Separating the necrotic bone from the overlying cartilage is a gap created by collapse of the bone trabeculae in the necrotic segment. E, Specimen radiograph demonstrates that the subchondral bone end plate remains attached to the articular cartilage, and around the margin of the infarct, the fracture extends through the bone end plate, producing deformity of the articular surface. F, Photomicrograph of a histologic section through the specimen (H&E, × 1 obj.). G, Photograph of the undersurface of a detached piece of articular surface with visible fragments of attached necrotic subchondral bone.
FIGURE 11-44  A, An osteopenic 57-year-old woman reported severe and intermitting pain in the right hip. B, There is evident flattening of the superior surface of the femoral head 1 month later, together with narrowing of the joint space. C, There has been further loss of joint space as well as bone 4 months later. This pattern of events is typical of rapidly destructive osteoarthritis.

FIGURE 11-45  A, A radiograph of a slice of the femoral head removed from the patient shown in Figure 11-44 demonstrates loss of tissue on the superior surface of the femoral head but no evidence of changes generally associated with osteoarthritis. In particular, there is a complete absence of osteophytes. B, A microscopic section shows apparent crushing of the bone trabeculae superiorly (H&E, × 1 obj.), which on closer viewing
FIGURE 11-45—CONT’D  (C) also reveals some immature fracture callus (H&E, × 4 obj.).  D, The attenuated trabeculae show focal resorption (H&E, × 10 obj.).  
E, In other areas, the marrow spaces are filled by immature callus (H&E, × 10 obj.).

FIGURE 11-46  A, In the deeper portion of the fracture shown in Figure 11-44, granulomas formed of amorphous debris surrounded by histiocytes and giant cells are present (H&E, × 4 obj.).  B, A higher power view to demonstrate the histiocytes and giant cells (H&E, × 25 obj.).
Thin, disconnected bone trabeculae indicative of osteopenia may be observed throughout the femoral head. Although focal thinning and/or absence of the articular cartilage has been noted at the superior portion of the femoral head, it is relatively well preserved on the other areas of the femoral head, with viable chondrocytes, indicating that there is no evidence of chondrolysis morphologically. The synovial tissue generally shows mild hyperplasia and hypertrophy, with minimal inflammation but massive focal accumulations of eosinophilic amorphous debris, including small pieces of bone and articular cartilage detritus (Fig. 11-47).

The initial clinicoradiologic findings in individuals with RDA are similar to those seen in cases of SIF. The mechanism of rapid joint destruction is almost certainly multifactorial, and no one factor is sufficient to explain it. Many factors may play an important role in the pathogenesis of rapid joint destruction, including increased levels of bone resorptive enzymes; however, the use of anti-inflammatory drugs or corticosteroid injection into the joint after the fracture has occurred may well play an important role.

We consider the granulomatous lesion to be the result of the rapid rate of bone destruction, which does now allow for resorption in the usual way.

The presence of SIF resulting from osteopenia should be kept in mind when elderly patients have hip pain. Preventive treatment for osteoporosis and the early recognition of SIF may contribute to the elimination of RDA.

**Osteochondritis Dissecans**

Osteochondritis dissecans is a benign noninflammatory condition of diarthrodial joints that affects young adults. The most commonly affected joints are the knee, ankle, and elbow. The disorder is characterized clinically by pain, limitation of motion, locking of the joint, or effusion. Imaging studies reveal a well-demarcated fragment of bone and overlying articular cartilage, which may or may not be separated from the articular surface at the time of presentation (Fig. 11-48). The condition usually involves the lateral aspect of the medial femoral condyle; less commonly, it involves the posteromedial aspect of the talus or the anterolateral aspect of the capitellum. Although osteochondritis dissecans is unilateral in most instances, rarely it may be bilateral and symmetrical.

Familial cases of osteochondritis have been reported, and in these patients, the disorder is probably transmitted as an autosomal dominant trait. Affected children are often short in stature and may have an associated endocrine dysfunction. In these patients, the underlying defect in osteochondritis dissecans may well be an accessory center of ossification, although trauma must play an important role in the initiation of clinical disease.

The gross appearance of a resected specimen is usually that of a flat, smooth nodule formed of avascular bone, with overlying viable articular cartilage. A layer of dense, fibrous connective tissue or fibrocartilage usually forms on the bone surface (Fig. 11-49).

Treatment consists of reattachment of the loose body (where feasible) or excision.
Slipped Capital Femoral Epiphysis (Adolescent Coxa Vara)

Slipped capital femoral epiphysis, a usual precursor of early-onset OA of the hip, is the result of a spontaneous fracture and disruption on the metaphyseal side of the growth plate of the femoral head. It usually occurs in overweight adolescent boys at the time of the growth spurt. The condition may be unilateral or bilateral. Early clinical symptoms and signs are pain or limping, with eventual limitation of mobility.

On radiographs, early displacement may be evident only on lateral films, where it appears as a backward (or dorsal) displacement (Fig. 11-50). Eventually, there is obvious separation of the femoral head and neck, with resultant coxa vara (Figs. 11-51 and 11-52). Valgus presentation is rare.

The condition is very common in domestic pigs that have been bred for very rapid growth. In these animals, the condition appears to result from the widening of the growth plate and the increase in vascularity that accompany the period of accelerated skeletal growth and is seen in several different joints.

Microscopically, the epiphyseal growth plate in an affected individual may appear markedly irregular and thicker than normal. Hemorrhage is often present between the growth plate and the primary spongiosa, thus effectively blocking the ingrowth of the metaphyseal capillaries into the growth plate and preventing endochondral ossification (Fig. 11-53). These circumstances would lead to an increased propensity for shear failure in the angulated growth plate of the femoral neck.

Treatment of a slipped epiphysis is generally by internal fixation of the femoral head.

In blacks, an increased incidence of chondrolysis has been reported in association with a slipped epiphysis. Patients with the combined disorder have elevated levels of immunoglobulins and the C3 component of complement. These findings suggest a localized antigen-antibody-mediated effect as part of a systemic disorder.

FIGURE 11-49 A, Radiograph of the knee in a 12-year-old boy who reported discomfort in the joint shows a well-demarcated defect on the articular surface of the medial femoral condyle. At this point, the osteochondral body has not separated from the condyle and is still in situ. B, Photograph of a section through a loose body removed from a patient with osteochondritis dissecans. There is a layer of intact articular cartilage on the lower surface with an overlying disc of attached bone, which itself has a fibrous covering on its inferior surface. C, Photomicrograph of the loose body. The bone may or may not be necrotic depending on whether or not it is still attached to the affected epiphysis (H&E, × 1 obj.).

FIGURE 11-50 Clinical radiograph of the hip joint in a patient with a significant slipped epiphysis. The inferior displacement of the capital femoral epiphysis on the neck of the femur can be readily appreciated.
Congenital Dislocation of the Hip

Congenital dislocation of the hip (CDH) is a relatively common abnormality in which the femoral head is not properly positioned in the acetabular fossa at the time of birth (Fig. 11-54). CDH is not a true congenital malformation, rather it results from either mechanical or physical factors that lead to instability of the hip in the newborn. These factors may include maternal hormones such as chorionic gonadotropin, maternal obesity, prolonged labor, and breech presentation. The exact mechanism by which these factors cause dislocation is not fully understood.

**Figure 11-51** Radiograph to demonstrate bilateral slip of the capital femoral epiphysis. On the left side, the epiphysis is almost completely dislocated with respect to the metaphysis.

**Figure 11-52** Photomicrograph of a section through the femoral head and neck of a case of slipped capital femoral epiphysis. The epiphyseal end of the bone has totally separated from the growth plate, a portion of which is seen on the outer surface of the lower left-hand side of the photograph (H&E, × 1 obj.).

**Figure 11-53** A. Low-power photomicrograph taken during an early stage of slipped epiphysis, before extensive displacement has occurred. On the left, focal thickening of the growth plate and separation of the growth plate from the underlying metaphysis by hemorrhagic tissue can be seen (Masson trichrome stain, × 4 obj.). B. High-power photomicrograph of the tissue in A shows focal hemorrhage between the growth plate and the metaphysis. It is postulated that such hemorrhagic tissue serves to block continued endochondral ossification, and consequently the growth plate becomes thicker owing to the lack of endochondral ossification and conversion to bone (Masson trichrome stain, × 25 obj.).
as estrogen and relaxin (which affect fetal as well as maternal ligamentous laxity), tight maternal abdominal and uterine musculature, breech presentation, or forced hip extension following birth. The left hip is more often involved, but bilateral dislocation is present in more than 25% of patients.

**FIGURE 11-54** Radiograph of a young child with untreated congenital dislocation of both hips. The roof of the acetabulum appears to be poorly formed. After reduction, this patient developed avascular necrosis of the right hip, a common complication.

**FIGURE 11-55** An anatomic dissection from a young child with congenital dislocation of the hip that was not reduced. Note the deformity of the femoral head, which has developed a saddle-shaped groove across its superior portion. On clinical radiographs, this groove may give the appearance of a double head.

**FIGURE 11-56** A, The upper end of the femur, whole and in coronal section, from a normally developed hip in a newborn. B, The upper end of the femur, whole and in coronal section, from an infant with hip dysplasia shows the abnormal configuration of the articular surface.
Treatment consists of early detection and reduction, that is, the return of the femoral head to its normal position as soon as possible after birth, and in those centers where this is routine practice, the condition is vanishingly rare. However, in persistent dislocation resulting from delayed diagnosis, the bone and soft tissue adjacent to the joint undergo reactive changes that preclude easy reduction. Both the acetabulum and femoral head become irregularly contoured (Fig. 11-55). Attempts at forcible reduction may compromise the blood supply and lead to avascular necrosis.

In untreated patients, secondary OA develops relatively early in life. In some patients, hip dysplasia (malformation of the joint) occurs without an obvious dislocation of the hip, and in such a case, there may have been a subtle degree of subluxation (Fig. 11-56).
### Chapter 12

The Inflammatory Arthritides

**Alfred Baring Garrod (1819–1907).** In 1848, he made his major contribution to our knowledge of the causation of gout. At a public lecture on February 8, 1848, which was reported in the Medical Chirurgical Transactions, he demonstrated the increase in uric acid in the blood of patients with gout. He also demonstrated deposits of urate in the articular cartilage of gout; however, it was not until 1960 that Hollander identified uric acid crystals in the synovial fluid in gout. (Photograph by Barraud. From the Wellcome Library, London.)

**Barbara Mary Ansell (1923–2001).** Barbara Mary Ansell was the doyen of pediatric rheumatology in England, particularly recognized for her work in defining different forms of idiopathic arthritis that commence in childhood and improving their management. She was author of more than 360 papers in adults and pediatric rheumatology. Ansell was a renowned lecturer and was an honorary member or fellow of more than 16 national and international societies. Among her British honors was the title of Commander of the Most Excellent Order of the British Empire, which she received in 1982. (From Hull R, Venning H: Dr. Barbara Mary Ansell, CBE, FRCP, FRCS, FRCPCH: 1923-2001, Arch Dis Child 2003;88:185, with permission from BMJ Publishing Group Ltd.)

### Inflammatory Arthritis Associated with Diffuse Connective Tissue Disease, 280

<table>
<thead>
<tr>
<th>Condition</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis, 280</td>
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<tr>
<td>Juvenile Rheumatoid Arthritis (Juvenile Chronic Polyarthritis; Juvenile Chronic Arthritis), 288</td>
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</tr>
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<tr>
<td>Bursitis, 289</td>
<td></td>
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### Diseases Resulting from Deposition of Metabolic Products in Joint Tissues, 289

<table>
<thead>
<tr>
<th>Condition</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Gout, 289</td>
<td></td>
</tr>
<tr>
<td>Lesch-Nyhan Syndrome, 291</td>
<td></td>
</tr>
<tr>
<td>Calcium Pyrophosphate Dihydrate Deposition Disease (Pseudogout, Chondrocalcinosis), 293</td>
<td></td>
</tr>
<tr>
<td>Examination of Synovial Fluid for Crystals, 298</td>
<td></td>
</tr>
<tr>
<td>Hemophilia, 299</td>
<td></td>
</tr>
</tbody>
</table>
Bacterial infections of the joint generally lead to severe and rapid breakdown of the tissues, with resultant severe arthritis (see Chapter 5, Joint Infection). The massive acute inflammatory infiltrate associated with pyogenic infection produces proteolytic enzymes that rapidly break down the articular cartilage and intra-articular structures (Figs. 12-1 and 12-2). Aspiration of the joint in such cases reveals a predominance of polymorphonuclear leukocytes, with a count usually greater than 100,000/mm³ (see Tables 10-1 and 10-2). Because both acute gout and acute rheumatoid disease, two of the principal topics of this chapter, also may present with fever and hot tender joints, on occasion it may be difficult to make the correct diagnosis; rarely infection may complicate pre-existing rheumatoid arthritis (RA), adding to the clinical diagnostic difficulties.

**Inflammatory Arthritis Associated with Diffuse Connective Tissue Disease**

Generalized polyarticular arthritis (rarely monarticular arthritis) is often the presenting symptom in patients with a variety of diffuse rheumatic connective tissue diseases such as RA, psoriasis, systemic lupus erythematosus (SLE), and Sjögren's syndrome.

Although the various rheumatic diseases differ markedly in clinical presentation, the histopathology of the associated joint disease tends to be similar. There are no specific qualitative microscopic findings in the synovium that distinguish RA from SLE or from the arthritis associated with psoriasis or ulcerative colitis. However, RA is the most common of these conditions and is most typically characterized by arthritis.

**RHEUMATOID ARTHRITIS**

RA, a much less common condition than osteoarthritis (OA), is a chronic systemic disease of unknown etiology that most commonly involves the synovial lining of both the peripheral joints and tendon sheaths; this inflammatory synovitis results in local destruction of the joint capsule and articular cartilage, ultimately leading to severe joint deformities (Fig. 12-3).
RA, which is two to three times more common in women than in men, is characterized clinically by spontaneous remission and exacerbation. Although it may occur at any age, the peak age of onset is the period from the fourth to the sixth decade. Of all affected individuals, 70% to 80% test positive for the histocompatibility antigen DW4 and/or DR4, a finding that implies a strong hereditary component. Extra-articular features, such as arteritis, neuropathy, pericarditis, splenomegaly, lymphadenopathy, and rheumatoid nodules occur with considerable frequency, indicating the systemic nature of the disease.

The affected patient is likely to report symptoms of general malaise, as well as pain and stiffness in the joints, characteristically more pronounced in the morning. Although any joint can be involved, those most commonly affected are the small joints of the hands and feet. In general, the disease is polyarticular, bilateral, and symmetrical.

Clinical examination reveals the acutely affected joint to be hot, swollen, and tender. Aspirated synovial effusion is milky and turbid (Fig. 12-4). Compared with septic arthritis, in which the synovial fluid usually contains more than 100,000 white blood cells/mm³ with at least 75% polymorphonuclear leukocytes, the rheumatoid joint effusion usually contains 20,000 to 50,000 inflammatory cells/mm³, with only about 50% polymorphonuclear leukocytes. Cultures of the synovial fluid and synovial membrane for various organisms, including viruses, have generally been negative.

The principal macroscopic morphologic feature of rheumatoid disease, seen both on imaging studies and at surgery, is joint destruction (Fig. 12-5). Unlike the noninflammatory arthritides, there is little reparative activity, and osteophytes and new bone formation are not prominent (Fig. 12-6).

Microscopically nonsuppurative chronic inflammation of the synovium is accompanied by hypertrophy and hyperplasia of the synovial lining cells, resulting in a papillary pattern at the surface of the synovium (Fig. 12-7). Often there are scattered giant cells among the synovial lining cells (Fig. 12-8). The subsynovial inflammation is characterized by an infiltration of lymphocytes, plasma cells, and some mast cells (Figs. 12-9 and 12-10). The plasma cells often contain eosinophilic inclusions of immunoglobulin (Russell bodies), lymphoid follicles may be prominent, and at the synovial surface, fibrinous
Section IV

Arthritis

Exudation with admixed polymorphonuclear leukocytes is a prominent feature, especially in the acute phase (Figs. 12-11 to 12-18).

In the course of the disease, the hypertrophied, inflamed synovium extends over the articular surface (pannus) and destroys the underlying cartilage by interfering with chondrocyte nutrition and by enzymatic degradation of the matrix (Figs. 12-19 and 12-20). The end result of this inflammatory destruction of the articular surfaces may be fusion of the joint (ankylosis), either by fibrous tissue or by bone (Figs. 12-21 and 12-22). In addition to destroying the cartilaginous surface of the joint, the rheumatoid synovium usually invades, weakens, and destroys the joint capsule and other periarticular supportive tissues. This leads to marked instability of the joint, frequently with subluxation or complete dislocation.

The inflamed synovium also invades the bone at the articular margins, a process that appears on radiographs as marginal erosions (Fig. 12-23). Extra-articular synovitis may lead to bursitis (Fig. 12-24), carpal tunnel syndrome or 'trigger finger,' or tendinitis (Fig. 12-25), and in some cases these clinical syndromes are the herald of more generalized articular disease later.

Joint destruction is not solely the result of intra-articular synovial inflammation. Within the marrow spaces of the subchondral bone, there may be considerable chronic inflammation and lymphoid follicle formation (Fig. 12-26). This inflammatory tissue is confined to the subchondral bone and does not extend far into the underlying cancellous bone. In many cases, the subchondral inflammatory tissue destroys the articular cartilage from below (Fig. 12-27) and it is possible to see cartilage destruction both on the articular surface by synovial pannus and from the subchondral bone (Fig. 12-28). Radiographs of affected joints usually reveal a juxta-articular osteopenia, which is probably the result of inflammation of the underlying bone.

**Figure 12-6** A, Frontal section through the femoral head in a patient with rheumatoid arthritis. Most of the articular cartilage has been destroyed, but there is no evidence of osteophyte formation or bone sclerosis. The absence of these two features is in marked contrast to the morphologic findings in patients with osteoarthritis. B, Specimen radiograph of A.

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**Figure 12-7** A, Photograph of synovium from a patient with rheumatoid arthritis. The cinnamon color is caused by posthemorrhagic hemosiderin deposits in the synovium. The plump papillae stem from the cellular overgrowth of the synovium, as well as from the lymphoid infiltration of the subintimal layer. The irregular white nodules on the surface are fibrin, the product of vascular exudation in the inflamed tissue. B, Photomicrograph demonstrating the hyperplasia of the synovial lining and subsynovial lymphocytic infiltration (H&E, × 4 obj.). C, A higher magnification of a section from B shows the synovial hyperplasia (H&E, × 40 obj.).
Figure 12-8 Photomicrograph of a section of synovial membrane from a patient with rheumatoid arthritis. The increased number of lining cells (hyperplasia) and their increased size (hypertrophy) are evident. Many giant cells are also present just below the surface. In the subintimal tissue, there is a chronic inflammatory infiltrate (H&E, × 10 obj.).

Figure 12-9 Photomicrograph of the subintimal region of the synovial membrane in a patient with rheumatoid arthritis shows infiltration of both lymphocytes and plasma cells (H&E, × 25 obj.).

Figure 12-10 Photomicrograph shows heavily stained basophilic mast cells within rheumatoid synovium (toluidine blue, × 25 obj.).

Figure 12-11 A. Photomicrograph of an inflammatory infiltrate of lymphocytes and plasma cells in rheumatoid synovium reveals eosinophilic cytoplasmic inclusions (Russell bodies) in many of the plasma cells (H&E, × 10 obj.). B. Higher magnification shows multiple accumulated Russell bodies in the cytoplasm of plasma cells (H&E, × 40 obj.).

Figure 12-12 The plasma cells and Russell bodies contain rheumatoid factor (immunoglobulin including immunoglobulin M), demonstrated here by staining with fluorescein-labeled antibody to rheumatoid factor. This specimen is viewed with ultraviolet light (and was one of the earliest demonstrations of an antigen-antibody reaction) (× 50 obj.).
Figure 12-14 Photomicrograph of the synovium shows focal fibrinous exudate on the inflamed synovial surface. The dark irregular fragments in the subsynovium are calcified bone detritus (H&E, × 10 obj.).

Figure 12-15 Photomicrograph showing polymorphonuclear leukocytes and nuclear debris in the fibrinous exudate of a patient with an acute rheumatoid joint. With this severity of acute inflammation, it is important to rule out an infection (H&E, × 10 obj.).
subchondral bone or by hyperemia secondary to the inflammation of the synovium (Fig. 12-29).

About 25% of patients with RA have subcutaneous nodules, which are most commonly seen over the extensor surfaces of the elbow and forearm (Fig. 12-30). Nodules may also occur in the gastrointestinal tract, lungs, heart, and the synovial membrane itself (Fig. 12-31). The nodules sometimes appear before other signs of rheumatoid disease have been recognized.

The rheumatoid nodule is characterized histologically by its irregular shape and a central zone of necrotic fibrinoid material surrounded by histiocytes and chronic inflammatory cells (Figs. 12-32 and 12-33). The long axes of the histiocytes are frequently radially disposed or palisaded around the necrotic core of the nodule. The fact that generalized vasculitis is common in patients with rheumatoid nodules is consistent with the belief that the nodules are the result of vascular damage.

Although the etiology of RA is unknown, two important factors contribute to its pathogenesis: an immunologic reaction and an increased number of degradative enzymes. The serum and synovial fluid of most patients with RA contain a number of immunoglobulins in common, the most frequent of which is immunoglobulin M. These immunoglobulins, known as rheumatoid factor, are produced by plasma cells both in the synovium and lymphoid system as antibodies to autologous immunoglobulin G, which in RA, is believed to be altered in some way. These factors appear on microscopic examination, both within and in the vicinity of plasma cells, as dense, homogenous, eosinophilic globules (or Russell bodies). Approximately 70% of patients with RA have a positive rheumatoid factor, and high titers may be associated with either acute disease or severe chronic disease.

Rheumatoid factor complexes with IgG in a manner not unlike an antigen-antibody reaction. Leukocytes are attracted to the immune complexes that, along with fibrin, form deposits on the surface of the inflamed synovium. These leukocytes, filled with particles of ingested fibrin and immune complex, may be found in the synovial...
FIGURE 12-19  A, Gross photograph of the radial head from a patient with rheumatoid arthritis. The hyperplastic papillary synovium extends onto and over the articular surface. B, The inflamed synovium forms a covering or pannus over the cartilage, which, in turn, is being eroded. Not only is the cartilage being eroded from the surface but the chondrocytes are themselves mostly necrotic with lysis of the surrounding matrix (Weichselbaum's lacunae) (H&E, × 4 obj.).

FIGURE 12-20  Photomicrograph of an articular surface in late rheumatoid arthritis, showing absence of the articular cartilage and a destructive fibrous pannus with resorption of the underlying trabecular bone and chronic inflammation of the marrow space (H&E, × 4 obj.).

FIGURE 12-21  Low-power photomicrograph of a metacarpophalangeal joint with a fibrous ankylosis (H&E, × 2.5 obj.).
fluid and are called RA cells. After destruction of the polymorphonuclear leukocytes, lysosomal enzymes are released into the extracellular space, where they further provoke an acute inflammatory response and tissue necrosis. These lysosomal enzymes exist in large concentrations in both the synovial fluid and tissue of rheumatoid joints, and they play an important role in perpetuation of the tissue destruction that characterizes the disease.

In the late stages of RA where the articular cartilage has been destroyed, the joint may show very little evidence of active inflammation though there may be some dystrophic calcification (Fig. 12-34).
Occasionally in histologic sections from patients with RA, it is possible to find evidence of the therapies used in the course of the disease such as gold and local corticosteroid injections (Figs. 12-35 and 12-36).

**Figure 12-26** Low-power photomicrograph of a section through a joint in a patient with rheumatoid arthritis. Note the extensive chronic inflammatory infiltrate in the subarticular marrow space, together with several lymphoid follicles on the left (H&E, × 2.5 obj.).

**Figure 12-27** A, Photomicrograph to demonstrate subchondral chronic inflammation in a patient with rheumatoid arthritis (H&E, × 5 obj.). A higher power view (B) to demonstrate the inflammatory destruction of the articular cartilage from its subchondral surface (H&E, × 25 obj.).

**Figure 12-28** Photomicrograph to demonstrate destruction of the articular surface by both pannus above and subchondral inflammation below. No articular cartilage is present (H&E, × 5 obj.).

**Figure 12-29** Radiograph of the elbow in a patient with polyarticular rheumatoid arthritis. Note the loss of joint space, resulting from destructive inflammatory synovitis. In this radiograph the soft tissue is clearly seen, making it apparent that there is considerable juxta-articular osteoporosis, a finding that is in marked contrast to the bony sclerosis associated with noninflammatory osteoarthritis.

**Juvenile Rheumatoid Arthritis (Juvenile Chronic Polyarthritis; Juvenile Chronic Arthritis)**

Chronic inflammatory arthritis may also occur in children. About 20% of cases are polyarthritis and present with systemic disease; 40% present with multiple joint involvement but without systemic disease; and 40% are pauciarticular without systemic disease. Most of these children test negative for rheumatoid factor; however, the few patients who are positive tend to pursue a more severe course and are more likely to end with a crippling arthritis. The outlook
for most children with juvenile rheumatoid arthritis (JRA) is good, and at least 75% of patients enter long remission with little or no residual disability.

Synovial biopsies in children affected by JRA usually show much less severe disease than the typical RA of adult onset (Fig. 12-37).

PSORIATIC ARTHRITIS

Perhaps less than 10% of patients with psoriasis have an associated inflammatory arthritis that, in general, is less severe than most cases of RA. Mostly, it is the peripheral joints that are involved by the disease—most often the distal interphalangeal joints.

Subcutaneous nodules are not a feature of psoriatic arthritis, although occasionally, they may be seen. However, these patients are usually found to have rheumatoid factor and the two diseases are generally considered coincidental.

The characteristic radiographic features in patients with psoriatic arthritis include destructive changes affecting small joints characterized by severe erosions resulting in a pencil-in-cup appearance (Fig. 12-38). In a few cases, there is a very severe mutilating process. Occasionally, there may be periostitis along the shafts of the long bones and prominent syndesmophytes in the spine.

Microscopically, the synovium of psoriatic arthritis is similar to that of RA, although it may be somewhat more fibrotic.

BURSITIS

Inflammatory bursitis is clinically characterized by pain, redness, and swelling of one of the many synovium-lined bursae that lie between muscles, tendons, and bone prominences, especially around the joints. Sometimes extensive calcification may complicate a chronically inflamed bursa, which renders it visible on radiologic examination. Bursitis is most commonly the result of localized chronic trauma. It often occurs in the shoulders of professional athletes and in the prepatellar and infrapatellar bursae of those who frequently kneel (e.g., housewives and the religiously inclined). Bursitis may sometimes be observed as a complication of RA.

A bursa may also be involved in other conditions that commonly affect the synovial membrane (e.g., gout, synovial chondromatosis, or pigmented villonodular synovitis), and in the past, bursitis from infection was frequently due to tuberculosis.

On gross examination of an inflamed bursa, the wall of the bursal sac is usually thickened and the lining often appears injected and shaggy due to fibrinous exudation into the cavity (Fig. 12-39). The microscopic findings depend on the etiology, and the various diseases that might affect the synovium, including infection, should be carefully sought. However, in most cases of post-traumatic origin, scarring and chronic inflammation predominate.

Diseases Resulting from Deposition of Metabolic Products in Joint Tissues

GOUT

Gout is a disease that has been commonly associated with rich living, obesity, heavy alcohol intake, hypertension, and renal disease. The condition is characterized clinically by episodic acute attacks of
inflammatory arthritis, usually monarticular, by the development of deposits of sodium urate around affected joints (tophaceous gout) and the development of renal calculi.

Uric acid is the end-product of the catabolism of purines, and because humans lack the enzyme uricase, increased synthesis of uric acid or decreased secretion of uric acid by the kidneys leads to hyperuricemia. It has been shown that both hypoxanthine-guanine-phosphoribosyl-transferase deficiency and phosphoribosyl-pyrophosphate synthetase overactivity can cause urate overproduction. Because uric acid is not very soluble, it begins to precipitate as sodium urate at concentrations higher than 8.0 mg/dL, especially in a more acid environment such as in the kidneys and joints. Prolonged hyperuricemia eventually leads to the deposition of monosodium urate crystals in both the joints and in the kidneys; occasionally in severe cases, other visceral organs may be affected. When crystals are precipitated in joint cavities, they may provoke an acute inflammatory response.

In most cases, hyperuricemia is secondary to disorders that either increase the production of uric acid by cell breakdown or decrease the excretion of uric acid as in chronic renal disease. The former group includes the myeloproliferative disorders, in which there is an increased turnover of nucleic acid, and cancer, in which there is increased cell breakdown.
Clinical gout can be divided into three stages: acute gouty arthritis, an intermediate stage called intercritical gout, and the chronic stage, in which diffuse deposits are seen (chronic tophaceous gout).

Acute gouty arthritis is usually monarticular and characterized by the rapid onset of very severe pain and swelling, often accompanied by a low-grade fever and leukocytosis. It has a particular predilection for the lower extremities. The first metatarsophalangeal joint (the great toe) is the most common site of initial involvement. Acute attacks may be precipitated by trauma, intercurrent illness, or debauchery.

Between attacks of acute gout, the patient may have long clinically asymptomatic periods, even though the hyperuricemia persists. Eventually the state of chronic tophaceous gout occurs, in which deposition of monosodium urate crystals occurs throughout the body but particularly in the kidneys and para-articular regions (Fig. 12-40). Although the reason for the deposition of crystals is not completely understood, the process is known to be accelerated by the presence of a low pH, as is present in the joint spaces.

The radiographic features of gout include swelling of the periarticular soft tissues and subsequent erosion of the periarticular bone, giving rise to the classic punched-out lesion with overhanging edges at the joint margin. Generally, there is little reactive sclerosis and, in contrast to RA, there is no regional osteoporosis (Figs. 12-41 and 12-42).

In acute gouty synovitis, microscopic examination of the synovial fluid reveals an inflammatory exudate that may be mistaken for infection. However, examination using polarized light and a first-order red filter will reveal crystals with a strong negative birefringence. Characteristically the crystals are found in polymorphonuclear leukocytes (Fig. 12-43). (A discussion of examination for crystals occurs later in this chapter.)

Lesch-Nyhan syndrome is a rare condition also characterized by the overproduction and accumulation of uric acid. In addition to the
SECTION IV ARTHRITIS

Figure 12-38 Radiograph of the right hand from a patient with psoriasis. Destructive lesions are present, particularly the distal interphalangeal joints. (Courtesy of Dr. Robert Freiberger.)

Figure 12-39 Cross photograph of an excised popliteal cyst, which was opened to demonstrate a thick fibrous wall with a roughened lining, and an overlying fibrinous exudate.

Figure 12-40 A, Photograph of a partially dissected finger amputated from a patient with gout. The large chalky white deposits are monosodium urate crystals. B, Photograph of sagittal section through finger shows destruction of the proximal interphalangeal joint. C, Specimen radiograph.
symptoms of gout, these patients have problems with the nervous system and behavioral disturbances. Abnormal involuntary muscle movements such as flexing, jerking, and flailing are often displayed. People with Lesch-Nyhan syndrome usually cannot walk, require assistance sitting, and are generally wheelchair bound. Self-injury, including biting and head banging, is the most common and distinctive behavioral problem in those with Lesch-Nyhan syndrome.

This condition is inherited in an X-linked recessive pattern. Mutations in the HPRT1 gene cause a severe deficiency of the enzyme hypoxanthine phosphoribosyltransferase 1, the enzyme responsible for recycling purines, which are building blocks of DNA and RNA. When this enzyme is lacking, the breakdown of purines results in abnormally high levels of uric acid in the body. However, it is unclear how a shortage of this enzyme causes the neurologic and behavioral problems characteristic of Lesch-Nyhan syndrome.

**CALCICM PYROPHOSPHATE DIHYDRATE DEPOSITION DISEASE (PSEUDOGOUT, CHONDROCALCINOSIS)**

As already discussed in Chapter 8, most cases of calcium deposition seen by imaging soft tissues are due to calcium hydroxyapatite; they occur either as a complication of trauma with associated necrosis

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FIGURE 12-41 A, Radiograph of the great toe shows involvement of the first metatarsophalangeal joint with gout. Overlying the joint there is soft tissue swelling, and at the joint margin a clear-cut bone erosion with a characteristic overhanging edge. There is no porosis of the surrounding bone, as would be seen in a patient with rheumatoid arthritis. B, Low-power photomicrograph of a portion of the joint shows erosion of the bone and articular cartilage by nodular deposits of sodium urate with an associated histiocytic and giant cell response (H&E, × 2.5 obj.).

FIGURE 12-42 A, Radiograph of a New York City pigeon. The soft tissue swellings are the result of tophaceous gout, which is not uncommon in these birds. B, Gross photograph of the affected feet, with a normal pigeon foot on the left for comparison. (Courtesy of Dr. S.K. Liu.)
Disease resulting from the deposition of calcium pyrophosphate dihydrate was first identified in 1962 in the synovial fluid of patients who had gout-like symptoms without sodium urate crystals, and consequently, this entity was designated as pseudogout by McCarty and his coworkers. The term chondrocalcinosis was introduced to describe a condition with typical radiologic evidence of calcification within the cartilage. However, because the condition may clinically be associated with many disease states, including gout, RA, OA, neuropathic arthritis, ankylosing spondylitis, hemochromatosis, and ochronosis, the term calcium pyrophosphate dihydrate deposition disease (CPPD) is perhaps more appropriate. CPPD is a disease of the elderly. Radiographic surveys have demonstrated an age-related increase in the prevalence of articular chondrocalcinosis, with an almost 50% incidence in people older than 80 years of age, which in the majority of cases are asymptomatic. There appears to be no major sex predominance, however, attacks of pseudogout seem to occur more frequently in men, whereas associated OA is more common in women.

Rare hereditary forms of CPPD are generally inherited in autosomal dominant mode. Specific gene mutations have been described in ANKH and COL. The ANKH gene has been shown to be involved in cellular transport of inorganic phosphate.

In some cases CPPD may be associated with other forms of metabolic dysfunction, such as hyperparathyroidism, hypothyroidism, gout, or hemochromatosis.

The most common clinical association of CPPD is that of OA, and symptomatic patients present with a progressive degeneration that

![Figure 12-43](image-url) Needle-shaped crystal in a synovial fluid sample. When this crystal was aligned with the indicator on the compensating filter, it demonstrated negative birefringence (bright yellow), which is consistent with a sodium urate crystal (× 100 obj.).

![Figure 12-44](image-url) A, Low-power photomicrograph of a tophaceous gouty deposit. A bluish amorphous material is seen surrounded by bundles of dense collagenized tissue and chronic inflammatory cells (H&E, × 4 obj.). B, The same field examined by polarized light. The birefringence of the crystalline material is evident. (Preservation of the crystals is improved by fixation in alcohol.) (H&E, × 4 obj.) C, Photomicrograph shows a detail of the field shown in B. Surrounding the amorphous crystalline deposit is a thin layer of mononuclear and giant cells (H&E, × 25 obj., polarized light). D, Photomicrograph of another section that has been stained by de Galantha’s method for demonstration of monosodium urate crystals (× 10 obj.).
Chapter 12

the inflammatory arthritides

often affects several joints. In order of frequency of involvement, the joints most likely to be affected are the knees, ankles, wrists, elbows, hips, and shoulders. It is rare that the metacarpals or metatarsals are involved. What the causal relationship of CPPD is with that of the observed arthritis is not known.

Patients with pseudogout account for less than 25% of those who clinically present with CPPD. Like gout, pseudogout has an acute onset with marked inflammatory changes and swelling. However, it is likely to be less severe than gout, and often there are cluster attacks—a single joint will first be affected, and then satellite joints around it will become involved. Pseudogout, like gout, may be provoked by an associated illness or by trauma (including surgery), and examination of the blood may on occasion show hyperuricemia, further complicating the diagnosis.

Other clinical presentations that may be associated with CPPD include multiple symmetric involvements of the joints in a rheumatoid-like fashion, rapidly degenerating joint conditions similar to Charcot’s joints, and stiffening of the spine (usually a familial condition).

On radiographic examination, the deposits of CPPD are radiodense and thus are generally easily distinguished from gouty deposits, which are radiolucent. The radiodense deposits are characteristically seen in fibrocartilage (Fig. 12-46), but may also be present in hyaline cartilage. The deposits are punctate or linear, and in hyaline cartilage, they usually parallel the subchondral bone end plate (Figs. 12-47 and 12-48). Punctate calcification may also be seen in the synovial tissue (Fig. 12-49). In addition to diarthrodial joints, the intervertebral discs and symphysis pubis are often affected. Chondrocalcinosis may be associated radiographically with joint space narrowing and bony sclerosis similar to that seen in patients with degenerative joint disease, but differing in location. The radiocarpal compartment of the wrist and the glenohumeral joint are commonly involved.

On microscopic examination, the chalky white deposits appear either crystalline or amorphous. In vascularized tissue, they may be surrounded by a chronic inflammatory and giant cell reaction (Fig. 12-50). In nonvascularized tissue, no inflammatory reaction is present (Fig. 12-51). The crystals are distinguished from gout crystals by their shape (rhomboidal) and by their weakly positive birefringence (Figs. 12-52 and 12-53). As is the case with gouty deposits, the crystals may not show up with polarized light in stained sections but are perfectly visible in unstained sections (Fig. 12-54).

Most investigators who have studied chondrocalcinosis believe that the crystal deposition has a chondrocytic origin, at least in the articular form. The earliest changes involve the cartilage lacunae, which become enlarged and coalescent. The adjacent matrix is replaced by chondromucoid material from which the cells ultimately disappear (Fig. 12-55). The characteristic calcified punctate lesions come about through the deposition of crystals in these

FIGURE 12-45 Lateral radiograph of the elbow of a patient with dermatomyositis. Extensive subcutaneous and soft tissue calcification is present. (Courtesy of Dr. Robert Freiberger.)

FIGURE 12-46 A, Radiograph of a knee joint in an elderly individual with extensive calcification of the menisci. B, Gross appearance of a meniscus with marked calcium pyrophosphate dihydrate deposition. C, A radiograph of this specimen.
Figure 12-47 A degenerated patella with extensive deposits of chalky white material identified as calcium pyrophosphate both on the surface of the cartilage, as well as in the synovium.

Figure 12-46—Cont’d D, Detail of the gross specimen meniscal margin.

Figure 12-48 A, Radiograph of a slice taken through the femoral head of a patient with hemochromatosis shows extensive calcification of the articular cartilage. B, In this cut surface of the femoral head, chalky white deposits of calcium pyrophosphate dihydrate can be seen in the depths of the cartilage. C, Specimen radiograph shows radio-opaque calcium deposits.

Figure 12-49 A, Synovial tissue in a patient with calcium pyrophosphate dihydrate deposition disease, with extensive calcific deposits immediately at the surface. B, Histologic preparation of the tissue, which has been stained with a von Kossa stain to demonstrate the calcium deposits (von Kossa, × 1 obj.).
FIGURE 12-50 This photomicrograph shows a deposit of calcium pyrophosphate dihydrate on the joint margin. The deposit is surrounded by mononuclear histiocytes and giant cells seen upper left, which gives the lesion an appearance very similar to that seen in patients with gout (H&E, × 10 obj.).

FIGURE 12-51 Photomicrograph of a deposit of calcium pyrophosphate dihydrate deposition disease in the meniscus. Note the absence of any inflammatory response (H&E, × 10 obj.).

FIGURE 12-52 Scanning electron photomicrograph of a deposit of calcium pyrophosphate dihydrate deposition disease, showing the characteristic rhomboidal crystals (× 2,400).

FIGURE 12-53 Photomicrograph of a deposit of calcium pyrophosphate dihydrate deposition disease crystals examined using polarized light and a first-order red compensating filter. When aligned with the compensating filter, the crystals are faintly refractive and blue (weak positive birefringence) (× 50 obj.).

FIGURE 12-54 Photomicrograph of an unstained section taken using polarized light, showing the refractive properties of the calcium pyrophosphate dihydrate deposition disease crystals (× 10 obj.).

FIGURE 12-55 Photomicrograph of a portion of articular cartilage demonstrates the appearance of the mucoid pools around the chondrocytes associated with the deposition of calcium pyrophosphate dihydrate deposition disease (H&E, × 25 obj.).
chondromucoid pools. It is thought that the deposits are finally released into the joint, where they may produce an inflammatory reaction.

There have been occasional reported cases of massive focal CPPD crystal deposition disease (tophaceous pseudogout) in atypical locations for CPPD, such as the temporomandibular joint and digits. Most commonly, the patients were older women who presented with a periarticular mass or swelling with or without pain. In these cases of tophaceous pseudogout, clinical and radiographic evidence of CPPD crystal deposition disease in any other joints is usually not present. Radiographs have shown calcified lesions with a granular or fluffy pattern. Histologically, the lesions have shown small or large deposits of intensely basophilic calcified material containing needle-shaped and rhomboid crystals with weakly positive birefringence characteristic of CPPD. Foreign body granulomatous reaction to the CPPD deposition was constantly found. Chondroid metaplasia in and around the areas of CPPD deposition has been commonly observed, sometimes with cellular atypia in chondrocytes, suggestive of a malignant cartilage tumor. It is important to recognize this rare form of CPPD crystal deposition disease and to identify the CPPD crystals in the calcified deposits and thereby avoid the misdiagnosis of soft tissue chondrosarcoma (Fig. 12-56).

EXAMINATION OF SYNOVIAL FLUID FOR CRYSTALS

An important diagnostic procedure for the clinical diagnosis of crystal synovitis is examination of synovial fluid for crystals and identification of these crystals by polarized light microscopy. This examination requires a polarizing microscope with a compensating first-order red filter. With the red filter in position, the crystals in the synovial fluid should be aligned so that their long axis is parallel to the line drawn on the compensating filter, which is the axis of slow vibration (Fig. 12-57).

**FIGURE 12-56** A, Clinical radiograph of the great toe of an elderly female with a history of a painful mass over a prolonged period of time. This was initially diagnosed as a soft tissue chondroma or calcified bursa. Grossly (B), it was found to be formed mostly of a chalky white material. On microscopic examination (C), deposits of calcium pyrophosphate with a histiocytic and giant cell reaction were present (H&E, × 10 obj.). In many areas (D), there was a cartilaginous matrix associated with the lesion (H&E, × 25 obj.).
Sodium urate crystals are usually needle shaped and exhibit strong negative birefringence, that is, they appear bright yellow when aligned parallel with the line on the compensating filter. CPPD crystals are usually rhomboidal and they exhibit weakly positive birefringence, that is, when their long axis is aligned with the line on the compensating filter, they appear blue and much less bright than urate crystals (Fig. 12-58). It is important to remember that when a crystal is oriented at 90 degrees to the line on the compensating filter, it will appear the opposite color to which it appears when parallel. Furthermore, the shape of the crystal may be misleading, because pyrophosphate crystals are occasionally needle shaped, and urate crystals may be broken up into short, squared-off fragments (Figs. 12-59 to 12-61).

**HEMOPHILIA**

Hemorrhage into a joint space, resulting in a hot, painful, and swollen joint, is a commonly observed clinical complication of hemophilia. These bloody joint effusions can be precipitated by even minor trauma or stress, and typically involve the knees, elbows, and ankles. Chronic, even subclinical, bloody effusions into the joint spaces may eventually lead to a destructive arthropathy, characterized on radiographic studies by a narrow joint space, cartilage destruction, bone erosion, multiple juxta-articular cysts, and if the lesion has progressed over a long period of time, osteophytes (Fig. 12-62). Radiographs may also reveal a peculiar juxtaepiphyseal...
osteoporosis (Fig. 12-63). Bleeding into the periosteum sometimes gives rise to a large, eccentric pseudotumor (Figs. 12-64 and 12-65).

Chronic hemarthrosis due to hemophilia or other bleeding diatheses is characterized by copious iron deposition and a markedly hyperplastic synovium (Fig. 12-66). The hyperplasia and hemosiderin deposition are usually limited to the synovial lining cells, although proliferative changes in the subsynovial capillary bed may be dramatic. On the basis of gross examination of the synovium, the differential diagnosis may include RA, pigmented villonodular synovitis, and hemochromatosis. However, microscopic examination of the synovium in hemophilia-related destructive joint disease does not reveal the striking lymphoplasmacytic infiltrate that characterizes RA, nor is there the nodular proliferation of mononuclear and giant cells characteristic of pigmented villonodular synovitis (although on occasion these two conditions may be confused, even microscopically) (Fig. 12-67).
A characteristic finding in joints affected by chronic hemorrhage is a brown-green-black discoloration of the articular cartilage, which may be mistaken at surgery for ochronosis. Microscopic examination of the cartilage often reveals widespread necrosis of the chondrocytes, as well as hemosiderin deposits in the chondrocytic lacunae (Fig. 12-68). However, no iron pigment is seen in the extracellular matrix.

**FIGURE 12-64** Sagittal section through a knee with intra-articular hemorrhage and massive joint destruction obtained from a case of hemophilia.

**FIGURE 12-65** Radiograph of a large pseudotumor secondary to a subperiosteal hemorrhage in the distal femur of a hemophiliac.

**FIGURE 12-66** Photograph of synovium removed from the knee of a patient suffering from hemophilia. The staining with hemosiderin is apparent as a mahogany color. Also apparent is the papillary proliferation of the synovial lining.

**FIGURE 12-67 A** Photomicrograph of hemophilic synovium demonstrates hemosiderin deposition both within the synovial lining cells and in the chronically inflamed and fibrotic subsynovial tissue (H&E, x 10 obj.). **B** Photomicrograph of another field stained by the Gomori iron stain to demonstrate the distribution of iron in the tissue (x 10 obj.).
A, Photograph of the articular surface of the tibial plateau excised from a patient with hemophilia. Attached to the joint margin is a heavily pigmented papillary synovium. The articular cartilage has a greenish black discoloration. B, Photomicrograph of the articular cartilage to show hemosiderin deposition within the chondrocytes of hemophilic cartilage (Gomori iron, × 50 obj.).
Christian Georg Schmorl (May 1861–August 1932). Schmorl studied medicine in Leipzig and Freiburg. After qualifying, he trained in pathology at the pathological institute in Leipzig. Schmorl was appointed Professor in 1903. He attracted students from all over the world and became known universally for his book on histopathological methods, which went through 15 editions. Having written one of the early descriptions of myelofibrosis, in the last years of his life he devoted his time to studies of spinal disease, which he continued after retirement. While performing an autopsy, he contracted septicemia to which he succumbed on August 14, 1932. His book, *The Human Spine in Health and Disease*, was published shortly after his death. (Reproduced by permission from the Sächsische Landesbibliotek, Staats und Universitätsbibliothek Dresden, Dresden, Germany.)

Jacques Forestier (July 1890–March 1978). Born in Aux-les-Bains to a medical family, Jacques Forestier together with his father introduced gold therapy for the treatment of rheumatoid arthritis. He was an international rugby player and took part in the 1921 Olympics. A founding member of ligue contre le Rheumatism, he became the European president. He is remembered especially for his work on spondylitis. (From Kersely GD: Obituary, Dr. Jacques Forestier. Ann Rheum Dis 1978;37:388, with permission from BMJ Publishing Group, Ltd.)

Displacement of Disc Tissue, 304
Degenerative Arthritis, 310
Osteochondrosis, 310
Scheuermann’s Disease, 311
Spondylitis (Osteoarthritis of the Spine), 311
Neuropathic (Charcot’s) Spine, 312
Inflammatory Arthritis, 314
Rheumatoid Arthritis, 314
Inflammatory Spondyloarthropathies, 315
Ankylosing Spondyloarthropathies, 315
Ankylosing Spondylitis, 315
Ankylosing Hyperostosis of the Spine, 317
The vertebral column plays a central role in static and dynamic motor functions; it supports the head, shoulders, and arms, as well as the thoracic and abdominal contents, transmitting their weight to the pelvis. In addition the vertebral column protects the spinal cord and nerves, provides sensory orientation, and participates in the locomotion of the entire body. Each component of the vertebral column—vertebrae, intervertebral discs, muscles, and ligaments—contributes in different ways to its biomechanical function.

Because the spinal column contains more than 130 articulations, including both the solid intervertebral discs and the synovial joints of both the posterior articular processes and the vertebral articulations of the ribs, many pathologic conditions that affect the spine are arthritic; some processes affect the discs, whereas others, such as rheumatoid arthritis (RA), affect the diarthrodial joints. In general however, both the joints of the vertebrae and those of the arches are eventually involved.

This chapter discusses the different types of disc tissue displacement, degenerative arthritis, inflammatory arthritis, and finally, the ankylosing spondyloarthropathies.

**Displacement of Disc Tissue**

The intervertebral disc comprises a central nucleus pulposus consisting mainly of water and proteoglycan, which is confined within an annulus of obliquely oriented collagen fibers (see Chapter 1). Because water is incompressible, loads are transmitted hydrodynamically from one vertebra to the next through the cartilage and bony end plates, while radial forces are absorbed through the tension in the fibers of the annulus (Fig. 13-1).

The appearance of the disc alters with age. The disc of the young adult, with its bulging mucoid nucleus pulposus, dense collagenous annulus fibrosus, and well-defined cartilaginous end plates, can be clearly differentiated from that of the elderly person, with its shrunken, yellowed, and dehydrated appearance (Figs. 13-2 and 13-3).

If it is assumed that normal intradisc pressure exists in the standing position, then it has been estimated that a 5% forward tilt of the spine increases the pressure by about 25%. Sitting may increase it by about 40%, but lying supine reduces it by about half. Forward flexion of the spine may increase the intradiscal pressure by as much as 400%, demonstrating the importance of lifting with bent knees and a straight back (Fig. 13-4).

In general, acute displacement of the disc tissue following injury is a disease of young people in their third and fourth decades.
It is less likely to occur or to cause significant compromise of the neural canal or foramen in an older individual in whom disc tissue, especially the nucleus pulposus, is shrunken and dehydrated. Displacement of disc tissue (usually the nucleus pulposus) from the intervertebral disc space may occur anteriorly, posterolaterally, superiorly, or inferiorly (Fig. 13-5). (Posterior displacement is generally posterolateral because of the firm attachment of the posterior longitudinal ligament to the annulus of the disc. This is in distinction to the anterior longitudinal ligament, which is firmly attached to the vertebral body and only loosely attached to the disc.)

Displacement of disc tissue anteriorly produces spondylosis deformans, whereas displacement posterolaterally produces pressure on the nerve roots or encroachment on the contents of the spinal canal. Displacement superiorly or inferiorly, into the adjacent vertebral bodies, will lead to the development of Schmorl’s nodes.

The different forms of displacement include protrusion, prolapse, extrusion, and sequestration (Fig. 13-6). Protrusion is a bulging of the nucleus pulposus through a weakened annulus fibrosus, usually in a posterior or posterolateral direction; prolapse is a rupture of the nucleus pulposus through the annulus but not through the posterior or anterior longitudinal ligament; extrusion is a rupture of the nucleus pulposus through both the annulus and the ligament, usually the posterior longitudinal ligament; sequestration is a fragmentation of the extruded segment, occasionally with displacement of the free fragment into the spinal canal and often to a site removed from the point of rupture (Fig. 13-7). The inclusive general term “disc herniation” may describe either prolapse, protrusion, or extrusion. For displacement of the nuclear tissue to occur, there must be prior traumatic laceration of the annular fibers, which is usually associated with both torsion and compressive injuries resulting from the sudden application of load, frequently the result of incorrect lifting of a heavy weight.

Anterior protrusion (spondylosis deformans) is the most common form of disease seen both radiographically and at autopsy. By the age of 50, it is present in at least 50% of women and more than 60% of men; it is more likely to occur in people engaged in heavy physical labor. The lumbar spine is most commonly affected. Spondylosis
FIGURE 13-7 A, In this sagittal magnetic resonance imaging scan, severe degenerative change can be seen at the level of L4–L5. Behind the body of L2 is a large bean-shaped mass displacing the cauda equina. B, Cross-sectional imaging of the mass behind L2. C, Low-power photomicrograph of the material removed from the spinal canal at the level of L2 (H&E, × 1 obj.). D, Higher power reveals scar tissue and intermixed degenerated disc tissue (H&E, × 4 obj.). (Courtesy of Dr. Benjamin Hoch.)
defor\-mans is initiated by tears that occur anteriorly in the periphery of the annulus, where the collagen bundles attach to the vertebral bodies by Sharpey’s fibers (Fig. 13-8). This leads to anterior herniation of nuclear disc tissue and is potentiated by weight bearing and by spinal motion. Because the anterior longitudinal ligament has only weak attachments to the annulus, continuous tearing of these attachments by prolapsed disc material stimulates the development of beak-like bony outgrowths or spurs from the adjacent vertebral bodies (Fig. 13-9).

Posterolateral displacement is found at autopsy in approximately 50% of older individuals, mostly in the lumbar region of the spine. The basis for posterior disc displacement are small tears that accumulate in the annulus of the disc as a result of the injuries resulting from daily activities. These clefts, especially the radial ones, pave the way for displacement of the nucleus pulposus after acute trauma (Fig. 13-10). Disc material removed at the time of surgery usually displays evidence of degeneration, fraying of the collagen tissue and cellular necrosis, together with regenerative clones of chondrocytes; occasional granulation tissue and reparative fibroc- cartilage (Fig. 13-11). In general, it seems that chondrocyte proliferation in displaced disc material is much more prominent in younger subjects.

Displacement of disc tissue posteriorly and posterolaterally often causes clinical symptoms, depending on the amount of disc tissue

**FIGURE 13-8** Polarized photomicrograph showing the early development of spondylosis deformans, taken at the junction of the annulus fibrosus, subchondral bone, and anterior longitudinal ligament. At the insertion of the annulus into the bone is a linear tear through Sharpey’s fibers, providing a route for the herniation of nuclear material. The defect is partially filled with reparative fibrocartilage [polarized light, × 1.5 obj].

**FIGURE 13-9** A, Photograph of a sagittal section of a lumbar spine with spondylosis deformans at the L4–5 disc space, and an anterior traction osteophyte, compared with the levels above. B, A specimen radiograph.
Section IV

Arthritis
displaced and its proximity to neural structures. The typical clinical presentation is that of nerve root compression with radiating pain, which results from an immediate acute inflammatory response to the displaced disc tissue. After a period of bed rest, there is regression of edema and inflammation, and the pain usually subsides. Later recurrence of pain may result from further displacement of disc tissue or from scarring, which is sometimes accompanied by calcification and ossification. (The relative infrequency of osteophyte formation in the posterior aspect of the vertebral body is due to the firm attachment of the disc to the posterior longitudinal ligament.)

Herniation of disc substance through the cartilaginous end plate into the adjacent vertebral body leads to the formation of Schmorl's nodes. These herniations, which are in most people probably traumatic in origin, extend for variable distances into the cancellous bone of the adjacent vertebral body. The clinical significance of Schmorl's nodes is that as disc tissue escapes into the vertebral bodies, the intervertebral disc becomes degenerated and thinned, thus causing displacement of the facet joints leading to osteoarthritis (OA) in those joints. Rarely when they are large and symptomatic, Schmorl's nodes may be misdiagnosed radiologically as tumors, and histologically misdiagnosed as chordoma or a cartilaginous tumor (Fig. 13-12).

Figure 13-10 A. Photograph of an L4–5 disc in cross-section after injection of contrast medium into the nucleus pulposus. Note extension of the dye posterolaterally. It is dissecting between the disc and the posterior longitudinal ligament, which appears to be intact. There is a bulging that results in an impression upon the dura, with narrowing of the intervertebral foramen (lateral recess). B, A computed tomography scan of the same specimen demonstrates the posterolateral bulging. C, Schematic drawing.
FIGURE 13-11  A, Photomicrograph of tissue removed at surgery from a herniated intervertebral disc. Note the irregular fibrillated matrix of the nucleus pulposus, which appears to be largely necrotic but has foci of proliferating cartilage cells characterized by intense basophilic staining (H&E, × 4 obj.). B, With extruded disc tissue, there is often an inflammatory response, as shown in this photomicrograph. The inflammatory granulation tissue will contribute to the nerve root compression (H&E, × 10 obj.).

FIGURE 13-12  A, Photograph of a segment of spine removed at autopsy demonstrates herniation of the intervertebral disc into the adjacent vertebral body. Such herniations are commonly found at the autopsy and are known as Schmorl’s nodules. B, Specimen radiograph of A. C, Photomicrograph of Schmorl’s node (H&E, × 4 obj.). D, At a higher magnification the cellularity of the cartilage could, in a clinical setting that had suggested a tumor, be misinterpreted as chondrosarcoma (H&E, × 25 obj.). (C & D Courtesy of Dr. Howard Dorfman.)
Degenerative Arthritis

OSTEOCHONDROSIS

Osteochondrosis is a clinical term used to describe the pathologic changes that occur in the intervertebral disc and in the adjacent bone of the vertebral bodies as a result of disruption in the region of the end plate of the disc.

Following disruption of the cartilaginous end plate, the other disc components exhibit rapidly progressive degeneration, with focal necrosis, fissuring, radial or circumferential tearing in the annulus fibrosus, and replacement of normal disc tissue by fibrous tissue. Large horizontal clefts may develop in the central part of the disc tissue and can be seen on clinical radiographs, where they are often referred to, incorrectly, as the vacuum phenomenon (Fig. 13-13).

Disc calcification is common. However, apatite crystal deposits can be easily overlooked in sections prepared with hematoxylin and eosin staining (Fig. 13-14). Calcium pyrophosphate dihydrate deposition disease (CPPD) is a frequent finding in surgical specimens both of disc tissue and in the ligamentum flavum (Fig. 13-15).

As disc degeneration progresses, with subsequent narrowing of the disc space, formation of new bone takes place around

**FIGURE 13-13** (A) Photograph of a sagittal section through L3–5 of a 72-year-old man. Note severe disc degeneration, along with irregularity of the end plates and adjacent sclerosis of the bone. **B,** Specimen radiograph of the portion of spine illustrated in **A.** Note the radiolucent line within the disc, which corresponds to the cleft seen in the gross photograph. This line is usually referred to by radiologists as the vacuum phenomenon.

**FIGURE 13-14** Photomicrograph showing focal pericellular calcium apatite deposits in the right hand third of the field (H&E, × 10 obj.).

**FIGURE 13-15** Photomicrograph of fragments of intervertebral disc tissue obtained at surgery, demonstrating islands of calcium pyrophosphate crystal deposition (H&E, × 4 obj.).
the periphery of the disc, at the junction of the annulus and the vertebral body resulting in marginal osteophytes. Ossification also occurs within the disc as a result of endochondral ossification of the cartilaginous end plate, contributing to narrowing of the disc space (Fig. 13-16). After vascular invasion, progressive breakdown of the disc tissue contents will lead to their resorption. Frequently, the final stage of the resorption process is a spontaneous bony fusion of adjacent vertebral bodies.

**SCHEUERMANN’S DISEASE**

Scheuermann's disease, also known as juvenile kyphosis, has its clinical onset in adolescence. It is characterized by an abnormal increase in the dorsal convexity of the thoracic spine (Fig. 13-17).

A hereditary component is involved in the development of the condition, but the mode of inheritance is as yet unclear. Reports of identical radiologic changes in monozygotic twins and of transmission over three generations supports inheritance, and in a study by McKenzie and Sillence, 12 probands were referred, and upon radiologic examination of their parents and siblings, seven were shown to have familial Scheuermann's disease with an autosomal dominant pattern of inheritance. Of the remaining five probands, four had chromosomal anomalies.

Although the pathogenesis of the disease is unknown, it is generally believed to be initiated by an abnormality in the development of the cartilaginous end plate. Lateral radiographs are most helpful in clinical diagnosis and classification. Anterior wedging of the thoracic vertebrae is characteristic, and irregularities of the vertebral end plates constitute a prominent feature (Fig. 13-18). Schmorl's nodes are characteristic, and narrowing of the intervertebral disc space occurs in the late stage of the disease. Concomitant with these changes is an increase in the thoracic kyphosis (beyond 40 degrees). The apex of the curve is usually around T7 to T9.

Characteristic anatomic findings in Scheuermann's disease include intervertebral disc narrowing and irregularly thinned cartilaginous end plates, with focal attenuation through which herniations of the intervertebral disc tissue extend into the adjacent vertebral body (Fig. 13-19). Narrowing of the disc is usually more pronounced anteriorly than posteriorly, possibly resulting in interference with growth of the vertebral ring epiphysis.

**SPONDYLOYSIS (OSTEOARTHRITIS OF THE SPINE)**

The term spondylolysis embraces the clinical disease resulting from degenerative disc disease (ostochondrosis), together with the associated vertebral osteophytosis, ligamentous disease, facet joint disease, and accompanying neurologic complications. Among middle-aged patients, it is one of the greatest single causes of morbidity. Anatomic evidence of OA of the spinal articulations is rare in subjects younger than 30 years of age. However, after the age of 45 years, OA becomes more common and is found at autopsy in more than 80% of spines from older individuals.

In the normal spine, the facet joints carry between 12% and 25% of the load. However, in the presence of disc narrowing from ostochondrosis, the load on the facet joints may increase to as much as 70%. Such excessive loads lead to the initiation of degenerative joint disease in the facet joints. The morphologic features of OA that are seen in other diarthrodial joints (i.e., capsular laxity, synovitis, cartilage fibrillation, cartilage loss with eburnation of the exposed bone, and marginal osteophyte formation) are all present in facet joint disease (Fig. 13-20), and it is likely that facet joint disease is a significant cause of low back pain.

Degenerative spondylolisthesis, the displacement of a vertebral body on the one directly below it, results from degeneration of the facet joints, which, in turn, is caused by narrowing of the intervertebral disc space. The end result of degenerative spondylolisthesis is stenosis of the spinal canal (Fig. 13-21). Although spondylolisthesis can occur in any spinal segment, it most often affects the more mobile segments of the spine (the cervical and lumbar segments).

Because the cervical portion of the vertebral column possesses the greatest mobility and has the greatest susceptibility to functional stress and trauma, cervical spondylolisthesis is very common and is often
debilitating (Figs. 13-22 and 13-23). Vertebral artery insufficiency is yet another potential complication that results from osteophytes impinging on the vertebral artery within the transverse foramina of C2 to C6. This complication is usually compounded by the presence of atherosclerotic vascular disease.

Lumbar spondylosis occurs most often in men and particularly affects the lower lumbar spine, where it represents one of the most common causes of low back and leg pain. Lumbar disc degeneration follows a chronic course, with repeated injury playing a precipitating role. These degenerative changes cause alterations in the size and shape of the vertebral canal and its lateral recesses, resulting in the development of spinal stenosis and subsequent nerve root compression (Fig. 13-24). The clinical manifestations include sciatica and/or ischemia of the cauda equina, with pseudo-(neurogenic) claudication.

### NEUROPATHIC (CHARCOT’S) SPINE

Trauma to the articulations, with their ultimate destruction, may occur as the result of impaired perception of pain or of proprioception (neuropathic arthropathy). Tabes dorsalis (neurosphillis), diabetes, syringomyelia, paraplegia, peripheral neuropathy, and congenital indifference to pain, as well as intra-articular steroid injections, are

![Figure 13-18](image-url) Lateral radiograph of a 13-year-old female with Scheuermann’s kyphosis. Note the wedging of the vertebrae at the apex of the curve and the irregularities of the end plates.

![Figure 13-19](image-url) **A**, Photograph of a sagittal section through the thoracic spine removed from a young patient with Scheuermann’s disease. Note the multiple end-plate irregularities as well as herniation of the disc tissue into the adjacent vertebral bodies. **B**, Specimen radiograph. Note the open vertebral ring apophysis.

![Figure 13-20](image-url) Sagittal section through L4–5 of a 79-year-old man shows severe narrowing of the facet joint, with associated subchondral sclerosis and osteophyte formation. Note the associated disc narrowing, posterior vertebral osteophytes, and lateral recess stenosis.
Chapter 13
Disc Disease and Spinal Arthritis

Figure 13-21 Lateral radiograph of the lumbar spine of a 58-year-old woman with back pain and pseudoclaudication. At L4–5, there is spondylolisthesis secondary to degenerative disc diseases. Note the narrowing of the spinal canal at that level. There is also severe disc narrowing at L2–3.

Figure 13-22 Photograph of the anterior oblique view of the macerated cervical spine of a 77-year-old woman. There is marked osteophyte formation of the uncovertebral joints, particularly in the lower cervical region. Note encroachment of the osteophytes on the intervertebral foramina, particularly at C5–7.

Figure 13-23 A macerated preparation of the cervical spine in a 74-year-old woman is shown externally in lateral view. Note the marginal osteophytes, which affect all of the facet joints.

Figure 13-24 Posterior oblique view of the lumbar spine of an elderly man, revealing severe facet joint arthritis. Note the exuberant marginal vertebral osteophytes with their irregular, serrated margins.
considered etiologic factors in the development of neuropathic arthropathy. In patients with tabetic arthropathy of the peripheral joints, 10% to 15% also have involvement of the lumbar spine (Fig. 13-25). In advanced cases, the spine may exhibit extensive disc destruction, with sclerosis and fragmentation of the vertebral bodies and massive osteophytosis. Histologic features include marked joint destruction, with bone debris in the synovial tissue and many loose bodies—changes similar to those seen in Charcot's joints elsewhere (Fig. 13-26).

**Inflammatory Arthritis**

**RHEUMATOID ARTHRITIS**

Approximately 60% to 70% of all patients with RA develop symptoms and signs relating to the cervical spine. Pain is the most common symptom; however, vertebrobasilar artery insufficiency may also occur, leading to transient blindness, vertigo, loss of consciousness and occasionally, sudden death. Radiographically, bone erosion and apophysial joint space narrowing are common, and may be followed by fibrous ankylosis and occasionally by bony ankylosis (Fig. 13-27). Erosions of the odontoid process secondary to inflammation of the transverse ligament occur in one third of patients with RA. As a result...
of such erosions, three major complications may occur: fracture of the odontoid after minimal trauma, disappearance of the odontoid if the erosion is severe enough, or atlantoaxial subluxation or basilar invagination (Figs. 13-28 and 13-29).

In the rheumatoid patient, it is important to recognize that secondary infections are also common, especially with the use of steroids and other immunosuppressive agents, and it is not unusual for such infections to be clinically silent.

**INFLAMMATORY SPONDYLOARTHRITIDES**

Inflammatory spondylitis might also be seen in patients who test negative for rheumatoid factor. Many of these patients have systemic disorders such as psoriasis or inflammatory bowel disease. The spondyloarthropathies are linked by common genetics (human leukocyte antigen [HLA] class-I gene, \( HLA-B27 \)) and a common pathology (enthesitis). Characteristically, the distribution and morphology of seronegative conditions are different from those of RA. Whereas in rheumatoid disease, the lesions are most obvious in the cervical region, in the seronegative spondylitides, sacroiliitis and involvement of the lumbar and lower thoracic spine are more common. Osteoporosis is not usually seen, and in marked contrast to rheumatoid disease, there is bony proliferation and occasionally intra-articular osseus fusion.

**Ankylosing Spondyloarthropathies**

**ANKYLOSING SPONDYLITIS**

Ankylosing spondylitis (AS) is the most prevalent of the spondyloarthropathies and primarily affects white men in their late adolescent or young adult years. Approximately 1% to 2% of all people who are positive for HLA-B27 develop AS, and this incidence increases to 20% if they have a first-degree relative with the condition. The onset of the disease is usually insidious, and its manifestations may evolve clinically in one of three patterns: in the axial skeleton, chiefly in the lumbar and sacroiliac joints; in
the peripheral large joints, predominantly in the hips, knees, and heels, especially among adolescents; or initially as recurrent iritis, aortic valvular disease, fatigue, and other systemic features, without obvious arthritis (Fig. 13-30). The spinal disease may eventually progress in an ascending fashion to involve the thoracic and cervical vertebrae, along with other axial articulations such as the ribs, resulting in a marked restriction of chest expansion. Either transient or chronic involvement of the peripheral joints has been reported in 50% of cases, especially in the hips and knees, but the small joints of the hands and feet are not commonly affected. The natural course of the disease is usually characterized by slow progression without periods of remission. Laboratory findings characteristic of the disease might include an elevated erythrocyte sedimentation rate (ESR), mild hypochromic anemia (in less than one third of cases), and elevated levels of serum creatinine phosphokinase (CPK) of muscle origin, which is seen in about one third of patients. Examination of the spine at autopsy of a patient with end-stage AS reveals fusion of the facet joints and intervertebral discs, resulting in a rigid, immobile vertebral column with accentuated kyphosis. However, ossification of the paravertebral ligaments is not a prominent feature (Fig. 13-31).

**FIGURE 13-30** Anteroposterior radiograph of the lower lumbar spine, pelvis, and hips of a man with advanced ankylosing spondylitis. Note generalized osteoporosis with fusion of the spinous process, intervertebral discs, sacroiliac joints, and symphysis pubis, and severe concentric degeneration with partial fusion in both hips. Thus, the entire skeletal unit has been transformed into one continuous osseous mass.

**FIGURE 13-31** A, Black and white photograph and (B) specimen radiograph of sagittal sections through segments of the vertebral column of a patient with ankylosing spondylitis. There is complete fusion of the spine with ossification of the intervertebral discs and the facet joints; note, too, the accentuated kyphosis with loss of lumbar and cervical lordosis. The deformity at the junction of the cervical and thoracic spine is due to a previous fracture. Closer images (C and D) show complete fusion of the apophyseal joints, as well as fusion across the intervertebral disc spaces. In this sagittal section through the lumbar spine, fusion of the intervertebral disc spaces is apparent. The paravertebral ligaments are spared, both anteriorly and posteriorly. (This is in marked contrast to ankylosing hyperostosis of the spine seen in Figure 13-32.)
Chapter 13
Disc Disease and Spinal Arthritis

Figure 13-31—Cont’d. E, Photomicrograph of a lumbar disc and adjacent vertebral bodies, taken from the upper part of (C), shows severe osteoporosis of the vertebral bodies. Fusion is mainly confined to the intervertebral disc, mainly in the region of the annulus (H&E, × 1 obj.).

Ankylosing Hyperostosis of the Spine

Ankylosing hyperostosis of the spine, also known as Forestier’s disease or diffuse idiopathic skeletal hyperostosis (DISH), is an ankylosis of the vertebral column resulting from ligamentous ossification without significant disc disease or facet joint involvement.

In Figure 13-32, an advanced stage of the disease is demonstrated, and in Figure 13-33, the earlier stages before complete fusion of the syndesmophytes. The diagnostic radiographic criteria include the presence of focal spinal ankylosis, intact vertebral end plates, normal intervertebral disc height and, most important, flowing ossification of the anterior longitudinal ligament at least four contiguous vertebral bodies, especially along the right side of the thoracolumbar region. Absence of facet joint and sacroiliac joint sclerosis and fusion differentiates the disorder from AS. Approximately one third of the older adult population has ankylosing hyperostosis at necropsy, more than half of these showing end-stage disease. Men are more commonly affected than women. The thoracic spine is involved twice as often as the lumbar spine, which, in turn, is involved twice as often as the cervical spine (Fig. 13-34). Dysphagia may be associated with cervical disease in some patients. Both fluoride intoxication as well as ‘excess’ vitamin A intake are believed to favor the development of DISH. Calcaneal spurs are found radiographically in about 90% of individuals with DISH, and occasionally, ossification at other tendinous insertion may be present.

A peculiar variant of cervical ankylosing hyperostosis has been described, particularly in the Japanese literature, in which ossification of the posterior longitudinal ligament occurs, sometimes leading to cord compression (Figs. 13-35 and 13-36).

In patients who have undergone total hip replacement, a higher incidence of heterotopic bone formation after surgery has been found in patients with pre-existing ankylosing hyperostosis (Fig. 13-37).

Figure 13-32. A, Photograph of a sagittal section through a segment of midthoracic and lower thoracic spine demonstrates ossification of the anterior longitudinal ligament, with consequent ankylosis of the anterior segment. Note that the disc spaces are relatively normal. B, In the same specimen, macerated, a thick plate of bone is seen lying along the anterior cortices of the vertebral bodies and extending in front of the intervertebral discs, like a layer of armor plating. C, Radiograph of the macerated specimen shows ossification of the anterior longitudinal ligament with intact vertebral end plates.
Figure 13-33  Radiograph of the lumbar spine to demonstrate various stages of syndesmophyte formation in a patient with diffuse idiopathic skeletal hyperostosis. Note that the facet joints are open.

Figure 13-34  Lateral radiograph of the cervical spine of an elderly male who complained of difficulty in swallowing. There is an irregular severe anterior hyperostosis, which is largely the result of ossification of the anterior longitudinal ligament, typical of diffuse idiopathic skeletal hyperostosis. Neither the disc spaces nor the facet joints appear fused and the bone is not osteopenic, thus ruling out a diagnosis of ankylosing spondylitis.

Figure 13-35  Photograph of a sagittal section through the cervical spine, which demonstrates both ossification of the anterior longitudinal ligament (diffuse idiopathic skeletal hyperostosis [DISH]) and severe ossification of the posterior longitudinal ligament (OPL).

Figure 13-36  CT scan of the upper cervical spine of a patient with ossification of the posterior longitudinal ligament and encroachment on the cervical canal. After minor trauma, this patient presented with myelopathy.
Figure 13-37  

A, Postoperative radiograph of a 65-year-old man following total hip replacement 3 years previously. Total bony ankylosis of the joint from ectopic ossification is seen. 

B, A lateral radiograph of the lumbar spine shows the anterior cortical hyperostosis and nonmarginal syndesmophyte formation typical of ankylosing hyperostosis (diffuse idiopathic skeletal hyperostosis).
Usual tissue response to clinically nonfailed articular implants, 326

- Cemented Implants, 326
- Noncemented Implants, 326

Morbidity associated with total joint replacements, 327

- Local Complications, 327
- Tumors and pseudotumors, 329
- Systemic Complications, 331

Tissue responses around noninfected, clinically failed articular implants, 331

- Cemented Implants, 332
- Noncemented Implants, 332
- Metal in tissues, 333
- Polyethylene in tissues, 334
- Methylmethacrylate in tissues, 334
- Silicone rubber in tissues, 335
- Ceramic in tissues, 335
Foreign materials, introduced into the human body by accidental trauma, have long been known to cause tissue damage and inflammation. Physicians, as a part of their therapy, also introduce foreign bodies in the shape of injected substances (corticosteroids, silicone, Synvisc), nails, screws, plates, drains and sutures manufactured of various metals, plastics, as well as organic materials, all of which might become infected (Figs. 14-1 to 14-4).

The determination to design artificial replacements for damaged or diseased skeletal parts, especially in the form of joint prosthesis, has resulted in the search for materials that can be implanted into the body without causing a deleterious reaction. This search for compatible materials has a long history, and many materials have been used, including gold, animal bone, ivory, and in the early attempts at joint replacement, lucite (Fig. 14-5).

Until the middle of the last century, the use of inorganic materials was restricted mostly to dentistry, although metal had been used for the internal fixation of fractures (Fig. 14-6). With the advances in artificial replacement of the hip joint by Charnley in the late 1950s, the use of metals and plastics by orthopaedic surgeons vastly increased. Millions of arthroplasties have been performed worldwide, and in the United States alone, it has been estimated that more
than 500,000 such procedures, including hips, knees, and other joints, are performed each year. Despite the success of the procedures, complications are eventually seen in about 10% of patients in the form either of loosening of the implanted part, which accounts for the majority of complications, or less commonly, infection. The major focus of orthopaedic research and development has been directed toward reducing this morbidity.

Prostheses for replacement of large joints, such as the hip and knee, often employ metal for the convex side of the joint (ceramic has also been used for this purpose) and high density polyethylene, with or without a metal backing, for the concave side of the joint. Polymethylmethacrylate (PMMA) is usually used as a grouting material to secure fixation (Fig. 14-7). This material is prepared from a mixture of liquid monomer, together with beads of fully...

**FIGURE 14-5** A Judet type prosthesis manufactured of lucite, which had been in place for many years before removal was deemed necessary.

**FIGURE 14-6** A, Photomicrograph shows a screw track in a femoral head. The thread is outlined by a thin layer of bone and fibrous tissue (H&E, × 1 obj.). B, A higher magnification of the boxed area in A shows the delicate fibrous cushion that has formed between the screw and its bony support (H&E, × 4 obj.).

**FIGURE 14-7** In this photograph, the components of a total hip replacement are seen to be well attached to the bone. A layer of cement is interposed between the prosthesis (the plastic acetabular component and the metal stem of the femoral component) and the bone to obtain a close, optimally immobile, fit of the prosthesis. Loosening of the prosthetic parts is a significant cause of failure in arthroplasty.
polymerized PMMA, and a small amount of particulate radiodense barium sulfate (or, recently, zirconium), for imaging the cement during postoperative follow-up (Fig. 14-8). Various metallic implants have been developed with porous surfaces to promote the ingrowth of bone and fibrous tissues into the prosthesis (Fig. 14-9). Implants of silicone rubber, which are not cemented in place, have been used for the small joints of the hand, wrist, and foot.

Experience indicates that there are essentially four types of responses in living tissues to implanted material:

1. If the material proves to be toxic, the surrounding tissues are damaged and might undergo necrosis and incite a severe inflammatory response;
2. If the material is nontoxic but is soluble, the surrounding tissues may remove and replace it;
3. If the material is nontoxic and biologically relatively inactive, as is the case with most materials used in the manufacture of prostheses, a capsule of fibrous tissue is formed around it (Fig. 14-10);
4. If the material is nontoxic but biologically active, a bond can form between it and the surrounding tissue.

In general the metals and other inorganic materials that have been used in orthopaedic implants abrade, corrode, or dissolve to variable degrees after implantation, producing both particulate debris and ionized constituents. With the use of moving parts, the generation of particulate wear debris has been the cause of the greatest concern with respect to loosening of the prosthesis as well as possible cytotoxic effects (Fig. 14-11).

The cytologic effects of the different metals used in orthopaedic implants, although minimal, are varied. In cell culture using murine peritoneal macrophages, Rae studied the effects of particulate cobalt, chromium, molybdenum, nickel, titanium, and cobalt-chromium alloy on the release of lactate dehydrogenase (LDH) and the activity of glucose-6-phosphate dehydrogenase (G6PD). These investigations showed that cultures exposed to particulate molybdenum, chromium, or titanium did not produce elevations in extracellular LDH or reductions in intracellular G6PD. However, cultures exposed to particulate cobalt, nickel, or cobalt-chromium alloy produced elevations in LDH and reductions in G6PD. Alterations in G6PD activity may contribute to increased delayed infections because of an effect on the efficacy of the inflammatory response. The macrophages that ingested particles of chromium or molybdenum showed no morphologic alterations, whereas those that ingested particles of cobalt or cobalt-chromium alloy showed shrunken cytoplasm and nuclear pyknosis.

Although there is little evidence that the fully polymerized PMMA is toxic to host tissues, the monomeric form has been shown to have local and systemic toxic effects, which will be discussed later. It has been hypothesized that biomedical polymers as a group, and polyethylene in particular, are capable of significantly affecting macrophage activation and production of interleukin-1.

In addition to their composition, the size, shape, and surface characteristics of implanted materials may have important effects on the surrounding tissue response (Fig. 14-12).
FIGURE 14-10 A. Photograph demonstrating the appearance after a cylinder of inert metal had been implanted in skeletal muscle for 6 weeks. B. Photomicrograph of a histologic section prepared from the specimen in A shows a very thin fibrous membrane around the space that was occupied by the metal implant (H&E, × 4 obj.).

FIGURE 14-11 A. Photograph of the articular surface of a removed femoral component of a total hip replacement. This component, manufactured from titanium, shows severe burnishing of the articular surface especially superiorly. B. Photomicrograph of the synovial tissue surrounding the joint reveals extensive deposits of black metallic debris within the synovial and histiocytic cells (H&E, × 10 obj.). C. High-power view of the metal-filled histiocytes (H&E, × 50 obj.).
Usual Tissue Response to Clinically Nonfailed Articular Implants

CEMENTED IMPLANTS

At the time of initial fixation with PMMA, a rim of necrosis a few millimeters thick develops in the adjacent bone. It is likely that this rim of necrosis results from a combination of direct physical damage to the bone, including disruption of the local blood supply, heat generated during polymerization, and possibly a toxic effect of any residual monomer. This is followed by the ingrowth of granulation tissue and osteoclastic removal of damaged bone, which might be seen as early as 1 week after implantation.

Implants recovered at autopsy show that securely fixed prostheses have a bone-cement interface of variable composition. Most of the interface consists of a thin fibrous membrane lying between the bone and the cement, which is usually thicker at surfaces that are subjected to compressive forces, such as those on the acetabular side of the hip and the tibial side of the knee (Fig. 14-13). Histologically this membrane is composed of densely packed collagenized tissue that, in some areas, may show fibrocartilaginous metaplasia. Small amounts of fragmented cement, macrophages, and chronic inflammatory cells may be present in the membrane. Occasionally the membrane undergoes complete osseous replacement, so that bone comes into direct contact with the cement. (This is most likely to occur at the more vertically oriented surfaces.)

The surface appearance of the cement mantle varies according to the type of bone tissue with which it comes into contact. In the femoral neck, where cancellous bone predominates, the cement mantle presents a nodular and papillary roughened surface, corresponding to the distribution of the bony trabeculae (Fig. 14-14). Distally in the femoral shaft, the cement comes into contact with the cortical endosteal surface, which is relatively smoother.

NONCEMENTED IMPLANTS

The interface of a noncemented implant has a variable morphology. Along the more vertically oriented smooth surfaces of, for example, a Thompson-Moore prosthesis, the interface is composed of a dense, fibrous membrane that is usually a few millimeters thick. The collagen fibers in this membrane are oriented parallel to the implant surface (Fig. 14-15). Cellularity is sparse, and consists mostly of fibroblasts and occasional aggregates of chronic inflammatory cells associated with bone detritus. An ill-defined layer of cells resembling synoviocytes may be present at the surface of the membrane in contact with the implant. Blood vessels are usually concentrated on the bone side and do not penetrate to the implant side of the membrane. Evidence of osteoclastic activity is not usually present.
The interface membranes at horizontal implant surfaces differ from those at the vertically oriented surfaces. Along the weight-bearing surfaces of the implant, a thick layer of fibrocartilage develops and is supported by a well-developed bony end plate that overlies cancellous bone. The fibrocartilage may be so well developed as to mimic the features of articular cartilage. A small amount of metallic debris may be seen in these membranes.

The appearance of the tissue on an implant with a coated porous surface also depends on the vertical or horizontal orientation of the bone-implant interface. In the vertically oriented regions, osseous tissue normally grows into the roughened surface of the implant without a well-defined intervening fibrous membrane (Fig. 14-16). On horizontal surfaces, a fibrous membrane is more likely to develop despite the roughened surface (Fig. 14-17).

**Morbidity Associated with Total Joint Replacements**

In recent experience, the overall long-term failure rate for hip and knee replacements is around 5% to 10%. The most commonly reported morbidities following joint replacement are listed in Table 14-1.

**LOCAL COMPLICATIONS**

**Infection**

The risk for orthopaedic device–related infection (ODRI) is less than 1% to 2%. However, the absolute number of patients with infection continuously increases as the number of patients with implants grows. Treatment includes long-term antibiotics and implant removal.

After implantation of a prosthetic device, all surfaces of the implant are immediately coated with a layer of serum proteins and platelets. The earliest and clinically the most important event is the ‘race for the surface,’ a contest between tissue cell integration and bacterial adhesion to that same surface.

Adherence of *Staphylococcus aureus* and other organisms to bioprosthetic materials is mediated by adhesion proteins such as fibronectin, fibrinogen, and so on. These communities of bacterial colonies enclosed in a self-produced polymeric matrix and adherent to an inert or living surface are known as biofilms. Bacteria in a biofilm exist in a slow-growing or starved state (i.e., stationary phase) and, consequently, are not easily killed by antibiotics. (It has been...
suggested that coating the surfaces of metal pins and plates with silver, which is known to have a potent broad-spectrum antibacterial activity, may lower rates of infection.)

About 25% of infected cases occur within 4 weeks of surgery. Subacute infections (about 25% of infected cases) occur within 1 year. Late infection (about 50% of infected cases) develops after 2 years of pain-free use (Table 14-2). The most common pathogens in the acute infections are shown in Table 14-3.

Because infection around an implant cannot usually be cured by antibiotic therapy alone, removal of the prosthesis and extensive local débridement may be required. No preoperative tests are consistently sensitive and specific for infection in patients who need a revision arthroplasty. The only consistent clinical finding is pain at the site of the implant. The erythrocyte sedimentation rate, C-reactive protein levels, and imaging studies results are highly variable.

**TABLE 14-2 Infection as a Complication of Total Joint Replacements**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Time of Onset after Surgery</th>
<th>Signs and Symptoms</th>
<th>Representative Microorganisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early postoperative</td>
<td>≤2–4 weeks</td>
<td>Persistent pain, fever, redness, swelling after surgery</td>
<td><em>S. aureus</em>, coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Subacute</td>
<td>≤1 year</td>
<td>Insidious onset</td>
<td>Coagulase-negative staphylococci, <em>Propionibacterium</em> species, anaerobes, <em>S. aureus</em></td>
</tr>
<tr>
<td>Late infection</td>
<td>&gt;2 years</td>
<td>Fever, pain, redness, swelling after a long period of wellness</td>
<td>Streptococci, <em>S. aureus</em>, gram-negative bacilli</td>
</tr>
</tbody>
</table>

**TABLE 14-3 Microorganisms Isolated from Orthopaedic Device–Related Infection**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>20–25</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>20–25</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>14–19</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>8–11</td>
</tr>
<tr>
<td>Streptococci</td>
<td>8–10</td>
</tr>
<tr>
<td>Anaerobes*</td>
<td>6–10</td>
</tr>
<tr>
<td>Enterococci</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
</tbody>
</table>

*Positive anaerobic culture depends on transport media used in operating room and microbiological technique.

**FIGURE 14-17** A photograph of the under surface of the tibial component shows tan fibrous tissue overlying the porous metal surface.

**TABLE 14-1 Morbidity of Total Joint Replacements**

<table>
<thead>
<tr>
<th>Time</th>
<th>Morbidity</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Intraoperative hypotension</td>
<td>Systemic</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>Nerve disorders</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
<td>Systemic</td>
</tr>
<tr>
<td>Late</td>
<td>Infection</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>Aseptic loosening</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>Systemic</td>
</tr>
<tr>
<td></td>
<td>Breakage of implant</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy</td>
<td>Systemic</td>
</tr>
<tr>
<td></td>
<td>Tumors</td>
<td>Local</td>
</tr>
<tr>
<td></td>
<td>Pseudotumors</td>
<td>Local</td>
</tr>
</tbody>
</table>

**MICROBIOLOGIC CULTURES**

The reference standard for diagnosing infection is the isolation of the responsible pathogen. However, in practice, microbiologic cultures are only moderately sensitive or specific for diagnosing an infected prosthesis. A very low inoculum, adherent bacteria, and the formation of small-colony variants of *S. aureus* may limit detection. Technical issues that can affect culture results include poor positioning of the aspiration needle or the addition of local anesthetic to the inflamed joint fluid.

Intraoperative cultures including tissue provide the most useful specimens for microbiologic cultures and are frequently used as the reference standard for diagnosing ODRI. Simple technical considerations, such as routine antimicrobial prophylaxis, delay in sending the specimens to the laboratory, failure to ask for anaerobe cultures, and sending early swabs instead of tissue, affect the ability to culture and isolate the microorganism. It is advisable to send a minimum of three specimens to the laboratory. The implant, if available, should also be cultured. (Sonication may increase the sensitivity of the culture technique by dispersing adherent bacteria.)

**HISTOPATHOLOGY**

Intraoperative frozen sections facilitate the diagnosis of ODRI and help to distinguish true infection from contamination (Fig. 14-18).
The accuracy of the technique depends on the experience and training of the histopathologist and the proper sampling of specimens from clinically inflamed tissue. Moreover, sampling errors may lead to false-negative results. The combination of two independent tests—histopathologic and microbiologic—allows a more accurate diagnosis and should be used as the current reference standard for diagnosing ODRI.

Technical Failure

Technical failure may be associated with malalignment of the implant and the placement of the methylmethacrylate cement (Fig. 14-19). Improper cementing technique has been reported as the cause of such diverse complications as penetration of the medial wall of the acetabulum, obstruction of the small bowel caused by adhesions around a bolus of PMMA cement, unilateral ureteral obstruction, and postoperative hematuria. Other reported complications following total hip replacement include delayed irritation of the sciatic nerve, false aneurysm of the external iliac artery, formation of various fistulas, and progressive dyspareunia.

Incorrect surgical alignment of the implant is a significant cause of fracture of the various components of the implant.

Malignant Tumors

In humans, a small number of primary malignant tumors have been reported in association with orthopaedic implants; however, the largest number of implant-related tumors have occurred in dogs (Fig. 14-20). Osteosarcoma, fibrosarcoma, and undifferentiated sarcoma are the most common types of tumor seen in both humans and the dogs. As of 2008, at least 48 cases of malignant tumor have been reported in patients who had undergone total hip or total knee arthroplasty (Fig. 14-21).

Pseudotumors

In the context of implant reactions, a pseudotumor is a space-occupying lesion resulting from the accumulation of particulate debris at or near the site of the implant.

The problem of pseudotumor formation plagued the early experience of Charnley when he used Teflon for the acetabular component of his total hip replacements. The problem largely disappeared after the introduction of high-molecular-weight polyethylene. However, reports of extensive reactions to large amounts of polyethylene debris in both total hip and total knee arthroplasties, with subsequent loosening resulting from endosteal bone resorption caused by the mass effect of the accumulating debris and its accompanying cellular response of macrophages and giant cells, still continue to appear in the literature (Figs. 14-22 and 14-23).

Pseudotumors in the bones of the wrist after replacement of carpal bones or joints by silicone rubber implants have also been reported (Fig. 14-24).
FIGURE 14-20  
A, Radiograph of the left tibia of a 13-year-old terrier dog previously treated by intramedullary nailing for fracture. One year later, a swelling appeared around the fracture site. B, Photomicrograph of the tumor shows an anaplastic osteogenic sarcoma (H&E, x 25 obj.). (Courtesy of Dr. S.K. Liu.)

FIGURE 14-21  
A, Radiograph of a 53-year-old woman who underwent total joint replacement 8 years previously for secondary osteoarthritis following congenital dislocation of the hip. Recent pain in the hip prompted radiographic examination, which revealed the periosteal reaction seen here. 
B, The resected specimen from the case illustrated in A shows a large tumor around the upper end of the femur. (The prosthesis has been removed.) 
C, Photomicrograph of tissue obtained from the tumor shows an osteosarcoma (H&E, x 10 obj.).
Chapter 14

Systemic Complications

Hypotension and Intraoperative Death

Transient hypotension developing as a reaction to monomeric methylmethacrylate seems to be fairly common during the instillation of methylmethacrylate; however, intraoperative death resulting from this complication is fortunately extremely rare.

Allergy/Hypersensitivity

Since the mid-1970s, attention has been drawn to the possibility that metals used in orthopaedic implants may induce a hypersensitivity reaction. However, the importance of sensitivity to metals in patients who receive metallic joint implants is not clear. In reports that suggest that hypersensitivity has a causative role in loosening, the implants had already failed clinically and the timing of development of the sensitivity was not known. Even when metal sensitivity can be proved, it may be dose dependent and, therefore, may result from the loosening rather than being its cause. Inflammation and necrosis, as will be discussed later, often accompany failure of an implant, and in these cases, the effects of hypersensitivity on the tissues may not be distinguishable from other causes of inflammation.

Tissue reactions due to hypersensitivity are difficult to evaluate histopathologically in implant sites because of surgical scarring and the small amount of inflammation usually present in the tissues surrounding most types of implants during the early to intermediate postoperative time period. Hypersensitivity reactions may also be difficult to distinguish from low-grade infections, especially when the organism cannot be isolated. However, generally hypersensitivity reactions are characterized by a heavy lymphoplasmacytic response.

Lymph Node and Pulmonary Spread

Autopsy studies have shown that careful dissection of the lymph nodal draining sites of replaced joints and adequate sampling of lung tissue usually reveals the presence of particulate debris originating from the joint components, whether metal, plastic, or ceramic (Figs. 14-25 and 14-26). The significance of these findings is not known.

Tissue Responses Around Noninfected, Clinically Failed Articular Implants

Fatigue fractures at the implant-bone interface or in the metallic or plastic components, as well as wear and tear on the articulating surfaces, are clear causes of failure of an articular prosthesis (Fig. 14-27). In this regard, the quality of the bone into which the implant has been inserted is clearly of importance. Osteoporosis or other metabolic disturbances of the bone tissue will significantly affect the strength of the bone-prosthesis interface. Alterations in geometry and mechanics that result from fatigue and wear in the components can, in turn, potentiate and accelerate the process of failure of the prosthesis.

FIGURE 14-22 Radiograph of the pelvis in a patient with total joint replacement of some years' duration. Recent pain prompted radiographic examination, which shows superior migration of the head into the polyethylene acetabular cup, and a lytic defect in the ilium. Histologic examination revealed an accumulation of polyethylene and cement, with an associated histiocytic response.

FIGURE 14-23 A, Section through the acetabulum of a dog several months after total hip replacement shows a juxta-articular tumor mass of yellowish gray tissue. B, Photomicrograph of a section through the specimen reveals large pink collections of fibrin, in which there was admixed cement and polyethylene debris, surrounded by histiocytes and chronic inflammatory cells (H&E, × 1.25 obj.).
That being said, all failed implants that have been cemented in place have particulate cement in the surrounding bone and soft tissues. In addition, it is usually possible to find particulate polyethylene and metallic debris.

**CEMENTED IMPLANTS**

The surfaces of the cement mantle in failed loosened implants are generally smooth, polished, and devoid of the surface irregularities that characterize the tight interlock with bone in stable implants. This smooth appearance is due to fragmentation at the unstable interface resulting in pulverization of both cement and bone, which then accumulate in the surrounding tissues (Fig. 14-28).

The most obvious feature observed after failure of a cemented implant is the presence of a thickened membrane around the cement. This membrane may measure up to several millimeters in thickness; it usually has a granular surface and a grumous, friable consistency (Fig. 14-29).

The microscopic features of the membrane include fibrosis, necrosis, and infiltrates of macrophages and lymphocytes (Fig. 14-30). Macrophages are usually concentrated at the surface adjacent to the cement and may form a layer that has been likened to a synovial lining. Fibrosis is usually concentrated on the bone side of the membrane. Necrosis may be distributed throughout the membrane but is frequently close to the cement side.

**NONCEMENTED IMPLANTS**

Aseptic loosened noncemented implants also develop a thickened membrane, which usually has a granular, roughened surface, and is friable and generally tan in color. There may also be regions of gray or black discoloration owing to metal debris. In our experience, failed
implants made of titanium usually have the blackest appearance. Microscopic examination shows the presence of variable amounts of necrosis, fibrosis, and cellular prosthetic debris infiltrates consisting mostly of macrophages.

**METAL IN TISSUES**

Metals are subject to chemical corrosion in the body, which results in coarsely granular brown-black debris often seen around plates and screws. However, much more common are metallic particles produced as a result of wear at exposed articular surfaces and fractures of the metallic component of joint prostheses (Fig. 14-31).

Microscopic examination of tissue sections from around metal implants, whether cemented or not, usually show sparse small, irregular black fragments measuring from 1 to 3 µm in greatest dimension. These fragments are opaque, but because of diffraction of light at their edges, they can be more clearly seen in polarized light. Many of the fragments are present within macrophages. However, in cases in which a metal component has fractured; metal on metal components articulate with each other; or the prosthesis is manufactured...
of Ti-Al-V alloy; the metallic debris can also be seen free in the necrotic or fibrous tissue (Fig. 14-32).

Ultrastructural studies demonstrate that many of the metal particles are in phagolysosomes and have a diameter of less than 0.5 µm, which is below the resolution of light microscopy (Fig. 14-33). The affected macrophages demonstrate a decrease in the endoplasmic reticulum and other distortions of cytologic ultrastructure.

### POLYETHYLENE IN TISSUES

Polyethylene debris is generated at the articulating surfaces by a number of mechanisms, including direct abrasion, three-body wear (often from entrapped particles of cement as has been illustrated in Fig. 14-27), and surface fatigue damage, which increases with time.

Microscopic examination shows a cellular infiltrate of macrophages and giant cells, which may either have a granulomatous pattern or be a confluent dense sheet of cells suggesting a giant cell type of tumor. The polyethylene, in the form of variably sized shards of glassy, refractile material, can easily be overlooked in transmitted light. However, examination under polarized light will readily and sometimes dramatically demonstrate their presence (Fig. 14-34). The largest pieces may be surrounded by a layer of fibrous tissue (Fig. 14-35); the smaller pieces are surrounded or engulfed by giant cells and large mononuclear macrophages (Fig. 14-36). Occasionally, many of the giant cells are seen to contain ‘asteroid bodies’ (Fig. 14-37).

Debris from a polyethylene component is usually concentrated in the immediate vicinity of the component, in the synovial, pseudo-capsular structures, and the joint margin (Figs. 14-38 and 14-39). However, it may also be seen in small amounts deep within the bone and bone marrow (Fig. 14-40).

Rarely, the polyethylene component may have been a composite of carbon filaments. In this case, it is possible to find fragmented carbon filaments in these tissues (Fig. 14-41).

### METHYL METHACRYLATE IN TISSUES

In histologic sections, methylmethacrylate is not seen because it dissolves in the solvents used to process tissues for paraffin embedding. In unstained frozen-tissue sections, however, the PMMA fragments are glassy and granular but are not birefringent in polarized light (Fig. 14-42). In paraffin sections, the particles of PMMA instead appear as cleared-out spaces of widely variable size (Fig. 14-43). The largest spaces are lined with giant cells and are partially filled with granular material, which can be shown by energy dispersive analysis (EDAX) to contain barium sulfate.

![Figure 14-26](image1)

**Figure 14-26** A. Photomicrograph demonstrates fine particulate debris in histiocytes within lymph nodes of a patient who had had a titanium implant (H&E, × 50 obj.). B. Examination with polarized light shows a bright reflective edge to the particles.

![Figure 14-27](image2)

**Figure 14-27** A. The tibial components of total knee prosthesis show extensive wear and scuffing on the articular surfaces of the polyethylene components. The material generated by this wear process is taken up by the synovium and may cause a considerable synovial reaction. Significant wear results from fragments of cement that are caught between the articular surfaces and ground into the polyethylene. B. Scanning electron photomicrograph shows cement particles buried in the polyethylene surface of the tibial component (× 50 magnification).
mixed with the PMMA to provide radiodensity (Fig. 14-44). Very finely particulate PMMA is probably responsible for the extensive collection of swollen histiocytes, without refractile material which are frequently present around failed cemented prosthesis (Fig. 14-45).

Over the past few years, barium in cement as a contrast material has been replaced by zirconium, which may be prominent around failed prosthesis and easily mistaken for debris from a metallic component (Fig. 14-46).

**SILICONE RUBBER IN TISSUES**

The inflammatory response to silicone debris in tissue is moderate to intense, and consists of lymphocytes, plasma cells, eosinophils, macrophages, and foreign body giant cells. The silicone debris is bosselated, pale yellow, and faintly refractile but not birefringent in polarized light. The particles range in size from 6 to 100 µm. The particles are usually intracellular but may also be free in the extracellular connective tissues (Fig. 14-47).

**CERAMIC IN TISSUES**

The major feature of the reaction around a failed ceramic implant is the generation of a thickened membrane with necrosis, fibrosis,
and macrophages similar to that seen in failure of the other types of implant. Small nonrefractile particles of debris, smaller than 5 µm in size, are numerous within the membrane and have a gray black appearance. These particles are generally found within macrophages; foreign body giant cells are not usually seen. By EDAX analysis, the particles can be shown to contain both aluminum and silicon (Fig. 14-48).

There are at least three consequences of the shedding of wear particles, from articulating implants, into the tissues. First, the total surface area of contact between the implant material and the biologic environment is enormously increased, thus facilitating the release of potentially toxic elements. Second, wear particles of suitable size may be phagocytosed and, because the volume of phagocytes is much greater than the volume of ingested material, the process results in a space-occupying lesion (pseudotumor). Third, particles that have been ingested may be transported to sites remote from the implant, such as regional lymph nodes, lungs, and spleen, and may interfere with the functions of these systems.

FIGURE 14-32  A, A portion of synovial tissue removed from around a failed prosthesis manufactured of titanium. Note the intense black discoloration of the synovial membrane. B, Photomicrograph of a section taken through the synovium. Particulate black debris is seen both intracellularly and extracellularly in a chronically inflamed fibrous tissue stroma (H&E, × 4 obj.). C, Another field that also contains foci of cement (H&E, × 10 obj.) and, on polarized light (D), can be seen to contain cement, polyethylene, and metal particles. E, Energy dispersive analysis shows a significant peak for titanium (TiKa and TiKb).

FIGURE 14-33 Electron photomicrograph of synovial cells from a patient with a total hip replacement shows an accumulation of electron-dense material in phagolysosomes in the cytoplasm. These dense particles are metallic (× 10,000).
FIGURE 14-34  
A, Photomicrograph of a histologic section taken from the synovium of a patient with a hip prosthesis in which the acetabular component was made of polyethylene. In the transmitted light photograph shown here, the subsynovium is infiltrated by large numbers of histiocytes and some chronic inflammatory cells (H&E, × 10 obj.). B, On polarized light microscopy, the cells are seen to be filled with threadlike particles of refractive material, which are derived from wear of the polyethylene surface.

FIGURE 14-35  
Photomicrograph demonstrates large pieces of polyethylene within the capsular tissue of a rapidly failing joint (H&E, partially polarized × 4 obj.).

FIGURE 14-36  
Photomicrograph of a giant cell reveals fine threadlike particles of polyethylene within the cytoplasm (H&E, Nomarski, × 25 obj.).

FIGURE 14-37  
Photomicrograph of a histiocytic and giant cell reaction to cement and polyethylene, showing the presence of asteroid bodies in two of the giant cells (H&E, × 40 obj.).
FIGURE 14-38 Photograph of synovium removed from a failed prosthesis showing marked papillary proliferation of the synovium with focal hemosiderin staining. Microscopic examination of this tissue revealed a foreign body reaction to polyethylene and cement debris.

FIGURE 14-39 A, Photomicrograph of a section taken through the articular surface of a patella from a removed total knee replacement. In the subchondral bone, there is a tumorlike accumulation of cellular tissue (H&E, × 4 obj.). B, High-power view of the tissue seen in A. Note histiocytic replacement of the bone and bone marrow (H&E, × 25 obj.). (Continued)
**FIGURE 14-40** Photomicrograph of a small granulomatous mass in the marrow space at some distance from the site of a prosthetic implant (H&E, × 25 obj.).

**FIGURE 14-41** Photomicrograph demonstrating cylindrical fragments of carbon fiber in the tissue from a patient who had a carbon fiber-reinforced implant. The section also shows a fibroblastic and histiocytic response, which with polarized light reveals extensive polyethylene debris (H&E, × 25 obj.).

**FIGURE 14-42** Photomicrograph of a specimen of synovium cut by frozen section without the use of solvents demonstrates cement in situ. Polymer balls are evident, and between these spheres, a finely granular yellow material is seen; the latter appearance results from the barium sulfate that is mixed with the cement to render it radiopaque (H&E, Nomarski, × 25 obj.).

**FIGURE 14-39—CONT'D** C, Polarized light microscopy reveals highly refractive particles of polyethylene debris within the histiocytes and giant cells of the tissue.
Figure 14-43 Photomicrograph demonstrating a giant cell reaction around a large piece of cement, which appears as an irregular space in the center of the photograph because the cement itself has been dissolved by routine processing methods. The small collection of granular material seen within the space is barium sulfate, which is mixed into the cement to render it radiopaque (H&E, × 40 obj.).

Figure 14-44 Photomicrograph showing a space that had contained a large piece of cement. The cement has been removed in processing, but there is residual particulate barium (H&E, × 10 obj.).

Figure 14-45 A, Photomicrograph of tissue obtained from around a lucent cemented prosthesis shows abundant foamy histiocytes (H&E, × 10 obj.). B, At a higher magnification, there is no obvious foreign body giant cell reaction (H&E, × 40 obj.).

Figure 14-46 (A) Photomicrograph to show zirconium particles within the tissue (H&E, × 25 obj.). (B) Close-up of zirconium particles, which are distinguished by their opacity jagged edges and central clearing (H&E, × 50 obj.).
FIGURE 14-47 Photomicrograph demonstrates breakdown products from Silastic prosthesis. There is a histiocytic and giant cell response in a fibrous scar tissue. An asteroid body is seen within a giant cell center field (H&E, Nomarski, × 25 obj.).

FIGURE 14-48 A, Photomicrograph of membrane adjacent to a failed ceramic prosthesis shows a gray-to-black discoloration of the tissue with secondary chronic inflammation and scarring (H&E, × 4 obj.). B, Photomicrograph of histiocytic response to ceramic. The ceramic particles are jagged in appearance and only faintly refractive (H&E, × 25 obj.). C, Energy dispersive analysis of the tissue shows peaks for aluminum and silica, consistent with ceramic (AlKa and SiKa).
Skeletal Manifestation of Decompression Sickness (Caisson Disease), 345

Bone Infarctions Not Associated with Caisson Disease, 346

Osteonecrosis of the Femoral Head, 346

Staging of Osteonecrosis of the Femoral Head, 348

Stage I, 348

Stage II, 349

Legg-Calvé-Perthes Disease, 355

Idiopathic, Nontraumatic or Primary Osteonecrosis of the Femoral Head, 358

Natural History and Diagnosis, 358

Etiology of Idiopathic Necrosis, 359
Tissue death (necrosis) results from one of five primary types of injury: (1) circulatory, (2) thermal, (3) toxic, (4) mechanical, or (5) radiation. When necrosis occurs secondary to a primary circulatory disturbance (arterial disease, embolism, or obstruction of the venous return), the resultant region of necrosis is referred to as an infarct.

Bone death, in the form of a sequestrum, was first recognized as a complication of osteomyelitis. Later it came to be recognized that necrosis occurred as a secondary event following fracture and that in certain locations such as the hip, patella, and carpal scaphoid, the associated necrosis could be so extensive as to give rise to significant clinical complaints of nonunion or secondary arthritis. The occurrence of bone infarcts in caisson workers and other divers who may get decompression sickness, as well as in patients with sickle cell anemia, Gaucher’s disease, and other hematologic disease, is now well recognized.

Many infarcts involve the femoral head or other convex articular surfaces. However, infarction affects other bone sites, usually the metaphysis of a long bone or even, on occasion, a flat bone. The lesions may be multiple and occasionally symmetrical. Most are asymptomatic and are discovered as an incidental radiologic finding.

The early stage of a bone infarct can be observed clinically only on magnetic resonance imaging (MRI) or at autopsy, where it appears as an elongated opaque pale yellow area with a hyperemic border that is rather sharply demarcated from the surrounding bones (Fig. 15-1). In the early stage, not enough time may have elapsed for changes in the architecture of the bone trabeculae to develop, and therefore, little if any change is seen on the radiograph. Microscopically, large irregular spaces are seen in ischemic marrow fat, which result from breakdown of the walls of fat cells (Fig. 15-2). The bone trabeculae are nonviable, as evidenced by lacunae that do not contain stainable osteocytes. However, the most obvious evidence of early infarction is seen in bone that contains hematopoietic tissue, since this tissue is extremely vulnerable to ischemia and the necrotic hematopoietic tissue is readily recognized (Fig. 15-3).

With the passage of time, ingrowth of granulation tissue takes place at the periphery of the infarcted area, and a ‘creeping substitution’ of the nonviable cancellous bone by layering of new viable bone on the dead trabecular surfaces takes place. With a small lesion, total healing may occur; however in most cases, the healing

---

**FIGURE 15-1** A, Photograph of a sagittal section through the lower leg and foot of a 68-year-old man with multiple sclerotic lesions radiographically and a nonunion of a fracture of the tibia. The multiple areas of sharply demarcated chalky white, opaque tissue in the tibia, talus, and os calcis are the result of infarction. B, Close-up photograph of cancellous bone demonstrates a small focus of marrow and bone necrosis recognized by its opacity, yellowish white color, and failure to retract like the surrounding viable fatty marrow.

---

**FIGURE 15-2** A. Photomicrograph demonstrates early fat necrosis resulting from ischemia. There is breakdown of the walls of the fat cells, resulting in large irregular cystic spaces that are surrounded by foamy histiocytes and giant cells (H&E, × 4 obj.). B, Higher power of the same tissue (H&E, × 20 obj.).
Bone infarction (osteonecrosis)

The process is aborted and a rim of highly collagenized connective tissue forms about the periphery of the lesion. This connective tissue wall generally becomes infiltrated with calcium salts (Fig. 15-4). Radiographs of lesions in the later stages of development have a typical appearance (Fig. 15-5). A moderately thick, radiopaque serpentine border may be observed, often outlining an elongated area of central relative radiolucency. This appearance when in long bones has been likened to a coil of smoke. In some cases, particularly in solitary lesions, radiographs may suggest a calcified enchondroma. However, usually the foci of calcified matrix in an enchondroma or chondrosarcoma are discrete and scattered diffusely throughout the lesion, and the margin of the lesion is not so clearly outlined as with an infarct. Some lesions that have been interpreted radiographically as bone infarcts may in fact represent calcified and cystified lipomas of bone (see Fig. 19-59).

The occasional development in a bone infarct of a primary malignant tumor, usually a malignant fibrous histiocytoma, is a well-recognized complication and is referred to again in Chapter 18.

Skeletal Manifestation of Decompression Sickness (Caisson Disease)

Decompression sickness is the consequence of the liberation of gas bubbles (notably nitrogen) in the tissues and blood of subjects who have undergone rapid decompression after a period of exposure to a hyperbaric environment. In a subject who is exposed to a hyperbaric environment, greater amounts of the various gases, which go to make up the air we breathe, enter into solution until a state of saturation of the blood and tissues has been reached. The time required for saturation is not the same for all tissues, and fat requires a much longer time before the saturation point for nitrogen is reached, because nitrogen is five times more soluble in fat than in water. If a person who has been in a hyperbaric (high-pressure) environment and whose blood and tissues are consequently saturated with the atmospheric gases passes from the hyperbaric environment too quickly to one of normal atmospheric pressure, then the various gases quickly come out of solution. By ventilation, the body readily disposés of the oxygen and carbon dioxide. On the other hand, the excess of nitrogen, which has come out of solution and which may form bubbles in the circulating blood can act as emboli, partially or completely blocking terminal vascular channels and giving rise to neurologic impairment. Because the accumulation of nitrogen is greatest in tissues rich in fat such as bone marrow, upon its release the pressure upon the regional blood vessels may obstruct the blood supply to the bone.

The acute manifestations of decompression sickness are “the bends,” consisting of pain (most often in the knees) and injury to vital organs (e.g., central nervous system, heart, lungs) due to bubbles of nitrogen arising or lodging in these organs. Organ damage may lead to permanent disability or even death.
The late effects of decompression sickness on the skeleton are the result of ischemic necrosis, and are observed particularly in bone sites rich in fatty marrow. Months or even years may elapse between the occurrence of the underlying bone infarction and the appearance of clinical and/or radiographic evidence of the bone necrosis (Fig. 15-6).

**Bone Infarctions Not associated with Caisson Disease**

Single or multiple bone infarcts within long bones that are not associated with caisson or sickle cell disease are uncommon.

Men and women are equally affected, and the average age is around 50 years. Many of the patients have an associated diffuse connective tissue disease, which has usually been treated with cortisone. In about two thirds of the cases, only a single bone is involved, whereas in the remainder multiple bones, often bilateral, are affected. The lesions have a predilection for the upper end of the tibial shaft and the lower end of the femoral shaft.

In approximately one half of the cases, it appears reasonable to attribute the patient’s symptoms directly to the lesion.

In 1915 Phemister described the microscopic findings in necrotic bone, comparing the changes in bone dying as a result of infection (septic necrosis) with those resulting from a circulatory interference following fracture (aseptic necrosis). Later, he reported the histologic and radiologic changes seen in dead bone, and the reparative processes occurring around dead bone, coining the term creeping substitution for the process whereby the dead bone is replaced by a layer of living bone that is deposited onto the pre-existing dead bone.

**Osteonecrosis of the Femoral Head**

Because the hip joint is a major focus of clinical orthopaedic interest, the bulk of the pertinent literature has centered on osteonecrosis of the femoral head.

Early writers on necrosis of the femoral head used the term aseptic necrosis to stress the absence of infection. Later, the term avascular necrosis was applied because most of the recognized cases were associated with subcapital femoral neck fracture, which would be expected to interrupt the blood supply to the femoral head. Subchondral osteonecrosis without a history of femoral neck fracture was considered unusual for a long time.

The relationship between the occurrence of idiopathic (i.e., without a fracture) subchondral necrosis and steroid therapy or alcoholism was slowly recognized during the 1950s to 1960s. Although a circulatory disturbance is assumed to be the principal primary mechanism of idiopathic necrosis in the bones, the location of the occlusion cannot usually be shown by anatomical dissection.

Recently, as discussed in Chapter 11, it has become clear that some instances of acute-onset arthritic disease of the hip joint, particularly in elderly individuals, which until recently would have been regarded on the basis of history and MRI to be cases of primary osteonecrosis of the femoral head, are due to subchondral fractures, often without any clear history of trauma. It was also thought at one time that most of that eponymous group of affections known as the osteochondritises, or osteochondroses, namely Kienböck’s disease, Köhler’s disease, Freiberg’s disease, Osgood-Schlatter’s disease, osteochondritis dissecans, and so on were due to bone necrosis, but it has become increasingly clear that many of these lesions are also
the result of trauma, which was often repetitive, with a resulting subarticular fracture. Necrosis is most probably the result of fracture, and therefore, a secondary phenomenon (Figs. 15-7 to 15-10). However, in some cases, it may be difficult to know which came first, necrosis or fractures, and such a case is shown in Figure 15-11.

At the present time in our laboratory, of the more than 2000 femoral heads removed each year during total hip replacement procedures for nontraumatic causes, nearly 10% show evidence of subchondral avascular necrosis as the primary etiology. Approximately 60% of the cases diagnosed as idiopathic osteonecrosis have bilateral disease, and most of these patients have a history of either corticosteroid use or of increased alcohol consumption.

Osteonecrosis as a secondary complication of osteoarthritis (OA) has been recognized grossly and confirmed microscopically in 38.2% of the femoral heads diagnosed in our laboratory as having primary OA. The foci of secondary osteonecrosis were categorized into two types based on shape, size and depth: a shallow flat lesion (median axis 3 to 10 mm, depth 2 to 3 mm) with or without cysts (368 cases, 36.5%), and a deep, wedge-shaped large lesion (> 20 mm across and depth 10 mm) with or without cysts (17 cases, 1.7%). In the shallow flat lesion, the age ranged from 25 to 88 years (average 66 years), the female-to-male ratio was 4:5, and the location of osteonecrosis correlated best with the direction of migration in osteoarthritis (Fig. 15-12). In the deep, wedge-shaped lesion, the age ranged from 56 to 92 years (average 70 years), the female-to-male ratio was 9:5, and the location of osteonecrosis was similar to that found in primary osteonecrosis (Fig. 15-13).

Fractures of the femoral neck occur predominantly in elderly persons frequently following a trivial injury; however, they are occasionally encountered in children and young adults. In young subjects, a complete fracture of the femoral neck may follow repetitive trauma and is likely to occur in young men undergoing basic military training or in other youthful subjects who are subjecting themselves to exceptional physical exertion, for example, shin splints in young ballet dancers.
A fracture of the femoral neck is regularly followed by more or less complete ischemic necrosis of the femoral head due to an interruption of its blood supply. However, even though the femoral head becomes necrotic, a majority of fractures treated by internal fixation unite with a sound bony union, sometimes within a few months. During this period, the necrotic head is in most cases undergoing revascularization and repair (Fig. 15-14).

Because the repair of the necrotic femoral head usually lags behind the healing of the fracture of the neck, perhaps it is not surprising that collapse of the upper weight-bearing segment of the femoral head constitutes a fairly common late complication, occurring in more than 20% of the patients with intracapsular fractures. This complication usually does not develop until about a year and a half after the occurrence of the fracture and sometimes is delayed for more than 2 years. The patient may have been ambulatory and free of pain for many months before the segmental collapse of the femoral head. However, the collapse results not only in pathologic incongruity of the articulating surfaces and therefore a dysfunctional joint, but also pain, which is often severe.

Stage I

In stage one, external examination of the joint shows no abnormalities, although an ill-defined focal yellow discoloration may be seen through the articular cartilage. On cut section of the femoral head, a necrotic wedge-shaped region in which the marrow is dull, yellow, chalky and opaque, will be seen. This is generally in an immediately subarticular location extending for some distance into the underlying epiphyseal bone. The region is usually well demarcated and

Staging of Osteonecrosis of the Femoral Head

In 1965, Catto published two classic papers describing in detail the destructive and reparative changes in subchondral avascular necrosis of the femoral head following fracture.

Four stages in the development of subchondral avascular necrosis were defined morphologically, and these four stages may be shown to correlate with the observed radiographic appearances:

- **Stage 1.** Characterized predominantly by the presence of necrosis of both bone and bone marrow without evidence of repair.
- **Stage 2.** Reparative processes are evident at the periphery of the necrotic region.
- **Stage 3.** The major feature is segmental collapse of the articular surface.
- **Stage 4.** Features of secondary OA have developed.

It is important to recognize that the morphologic features of subchondral avascular necrosis are a composite of both necrotizing and reparative processes, and that at least some of the apparently degenerative features—for example, segmental collapse in stage three—often may be the result of reparative processes.
separated from the surrounding bone marrow by a thin, red, hyperepic border (Figs. 15-15 and 15-16). The marrow beyond this border shows no specific abnormality referable to the necrotizing process, but may have an abnormal appearance depending on an associated or predisposing condition—for example, sickle cell disease with its dark red bone marrow, or Gaucher’s disease with its pale and waxy marrow. At this stage, changes in the trabecular architecture are not appreciable on specimen radiographs.

On microscopic examination, the overlying articular cartilage is viable. The subchondral bone, corresponding to the opaque yellow region seen grossly, is characterized by necrotic bone marrow, which is granular, eosinophilic, and lacking in cellular elements except for the occasional ghosts of disrupted fat cells. There may also be focally calcified lipid cysts (Fig. 15-17). In the bone, the osteocytic lacunae may be either empty, contain cellular debris, or have a ghost nucleus.

At the margin of the infarct, there is increased osteoclastic activity with removal of necrotic bone as well as an infiltration of proliferating fibroblasts and capillaries (granulation tissue) into the necrotic marrow. This zone corresponds to the thin red rim seen in the gross specimen. Beyond the infarct and the hypervascular zone, the bone and bone marrow are unchanged and reflect the state of the tissue before the necrotizing event.

**STAGE II**

As in stage I, the articular surface appears intact (Fig. 15-18). However, on sectioning the femoral head, a rim of bony sclerosis, best seen on specimen radiographs, can be identified at the boundary between the necrotic zone and the unaffected marrow (Fig. 15-19).

On microscopic examination an advancing front of granulation tissue, composed of lipid-laden macrophages, proliferating
fibroblasts, and capillaries is seen extending into the necrotic zone (Fig. 15-20). Following closely behind this clean up front is a second front where osteoblasts can be seen, depositing a layer of new bone on the pre-existing dead trabecular bone, called creeping substitution (Fig. 15-21).

The overall effect of these processes is to remove the necrotic marrow and bone while maintaining the structural integrity of the bone. The increased vascularity with osteoblastic activity and new bone formation give rise both to the clinical radiographic appearances of bony sclerosis at the margin of the infarct and to the increased uptake of radioactive technetium diphosphonate isotope on a bone scan (Fig. 15-22).

**Stage III**

An obvious alteration in the shape of the articular bone is first encountered in this stage (Fig. 15-23). This disturbance in shape is the result of fracture either within the necrotic region or at the junction of the necrotic bone and reparative tissue. It may be apparent on external examination of the bone as a buckling of the articular surface (Fig. 15-24). On sectioning the femoral head fracture can be seen to occur most often either just below the articular bone.
Calcification is sometimes a prominent feature in infarcted bone marrow and may on occasion give rise to increased density on radiographs (H&E, × 4 obj.).

**Figure 15-17** Calcification is sometimes a prominent feature in infarcted bone marrow and may on occasion give rise to increased density on radiographs (H&E, × 4 obj.).

**Figure 15-16** A. Section of a femoral head with stage I osteonecrosis. The infarcted area clearly outlined by a wide hyperemic border. B. Specimen radiograph of A, there is no change in the bony architecture. C. Photomicrograph of the infarcted bone and bone marrow reveals the acellular nature of the tissue and large, fat cysts characteristic of infarcted bone marrow (H&E, × 10 obj.).

**Figure 15-18** Diagrammatic representation of the changes that occur in stage II subchondral avascular necrosis.
FIGURE 15-19  

A, Photograph from a patient with stage II subchondral avascular necrosis shows a well-demarcated hyperemic border. A fine fracture line can be seen running through the necrotic bone close to the articular surface. B, Specimen radiograph showing a line of bone sclerosis that corresponds to the zone of hyperemia seen in the gross photograph. At the inferior edge of the infarcted area, there is a small fracture involving the subarticular bone, resulting in a small step deformity in the articular surface.

FIGURE 15-20  Photomicrograph demonstrates focal fat necrosis as well as fibroblastic and vascular proliferation at the margin of the infarced area (H&E, × 10 obj.).

FIGURE 15-21  In the process of healing an infarct of bone, a layer of living bone is deposited on the surface of the necrotic bone. This process, referred to as creeping substitution, gives rise to increased radiodensity at the healing margin of the infarct. Note the vascularized fibrous tissue in the adjacent marrow spaces (H&E, × 10 obj.).

FIGURE 15-22  Scintigram of the pelvis of a patient with symptoms suggestive of subchondral avascular necrosis, but without radiographic changes, shows increased uptake of isotope in the affected femoral head.
end plate, (i.e., superficial) (Fig. 15-25) or on the necrotic side of the advancing sclerosis in the reparative front (i.e., deep) (Fig. 15-26).

Fracture may be the result of the cumulative effect of microfractures induced by fatigue within the necrotic zone. On the other hand, it may be because of weakness of trabeculae in the reparative front because of increased osteoclastic resorption with interruption of trabecular continuity and associated inadequacy of repair bone. A focal concentration of stress, at the junction between the thickened sclerotic trabeculae of the reparative zone and the necrotic trabecula, resulting from the bioengineering concept of stress risers, may be yet another cause (Fig. 15-27).

**STAGE IV**

The major feature of this stage is articular deformity. Depending on the degree of bone loss and the severity of the deformity, it may be no longer possible on clinical radiographs to recognize the initial events as those of subchondral avascular necrosis. In many cases, however, there is sufficient evidence on gross and microscopic examination to allow for proper diagnosis (Fig. 15-28).

A frontal section of the femoral head at this stage of subchondral avascular necrosis may show residual fragments of articular cartilage and dense fibrous connective tissue in the area of infarction. The articular surface at the margin of the infarct will usually demonstrate a densely sclerotic eburnated articular surface (Fig. 15-29).

**FIGURE 15-23** Diagram illustrating the associated tissue changes with the crescent sign in stage III subchondral avascular necrosis.

**FIGURE 15-24** Gross photograph of a femoral head removed surgically after clinical signs and symptoms of avascular necrosis were detected. On the articular surface of the femoral head, there is a linear dimpling of the articular cartilage, marking the site of an underlying fracture.

**FIGURE 15-25** A, Radiograph of a young patient who complained of sudden onset of pain in the hip. In this frog lateral view, although the joint space is normal, a crescentic lucent zone outlining the articular surface can be seen on the superior aspect of the femoral head. This crescent sign is an early radiologic manifestation of avascular necrosis often best appreciated in the frog lateral view. B, Photograph of a slice taken through the femoral head shows that the subchondral infarct is demarcated from the viable bone by a zone of hyperemia. The lucent crescent seen on the radiograph in A represents the space between the articular cartilage and the underlying infarcted bone. This results from collapse of the subchondral bone following fracture in the zone between the infarct and the underlying viable bone; the more elastic articular cartilage maintains its contour.

(Continued)
Two useful clues to the diagnosis of subchondral avascular necrosis may be the absence of clearly eburnated bone at the articular surface overlying the area of infarction, and the presence of bony and cartilaginous debris in the accompanying synovial and capsular tissue. When the changes of secondary OA are advanced, the only clue that the initial event might have been subchondral avascular necrosis is that osteophytosis is less than expected and also that the femoral head may have a deep, saddle-shaped deformity.

In Figure 15-30 a rare case of an osteosarcoma is illustrated that was clinically mistaken for osteonecrosis of the hip.

Most of the recent imaging criteria for staging have developed from Catto’s classic description (Tables 15-1 and 15-2).
Legg-Calvé-Perthes Disease

Osteonecrosis of the femoral head also occurs in children, usually between the ages of 5 and 9 years. The disease is more likely to affect boys, and in about 13% of patients, the condition is bilateral. In some instances, a familial predisposition has been noted.

Injection studies have demonstrated that the most important vessels supplying the upper femoral epiphysis are the lateral epiphyseal vessels. Because the growth plate of the femoral head lies above the insertion of the capsule of the hip joint in children, the vessels track along the surface of the neck of the femur to enter the epiphysis above the growth plate. These vessels are therefore particularly vulnerable to interruption of blood flow by trauma or by increases in intra-articular pressure (Fig. 15-31). In Perthes disease, the ischemic events may be episodic in nature and result from intermittent increased intra-articular pressure.

One of the earliest radiologic signs of Legg-Calvé-Perthes disease is widening of the joint space. This is probably caused by the cessation of endochondral ossification and resultant failure of cartilage to be converted to bone. On the radiologic film, the continuous growth of the cartilage will be appreciated as an increase in the width of the joint space (Fig. 15-32). Although the necrotic bony epiphysis may undergo collapse and subsequent deformation,
FIGURE 15-29  A, Radiograph of a patient with severe hip disease secondary to subchondral avascular necrosis shows marked deformity of the superior margin of the femoral head secondary to collapse. B, A frontal section through the femoral head resected from the patient illustrated in A. C, Specimen radiograph of the case illustrated in A and B.

FIGURE 15-30  An anteroposterior radiograph of the right hip of a 56-year-old man who reported severe hip pain. The similarity of this image to Figure 15-29A is striking. However, in this case, a small primary osteosarcoma in the femoral head led to fracture and the superior portion of the head was displaced medially.
deformity may also result from the irregular growth of new bone as a result of revascularization at the surface of the necrotic secondary center of ossification (Fig. 15-33). Characteristic radiologic findings in patients with Legg-Calvé-Perthes disease include enlargement of the femoral head and sometimes alterations in the femoral neck. Because the growth plate is dependent upon the epiphyseal

![Figure 15-31](image-url) **FIGURE 15-31** Blood supply to the femoral head in a child.

![Figure 15-32](image-url) **FIGURE 15-32** In the early stage of Legg-Calvé-Perthes disease, there is cessation of growth in the bony epiphysis with continued growth of the cartilage. Therefore, radiographic studies reveal widening of the joint space. Interference with the vascular supply to the growth plate results in defects in the metaphysis, seen here as a lytic area on the lateral side of the left femoral head.

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### Table 15-1: Staging Osteonecrosis (University of Pennsylvania Classification and Staging)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal or nondiagnostic radiograph, bone scan, and MRI</td>
</tr>
</tbody>
</table>
| I     | Normal radiograph; abnormal bone scan and/or MRI
|       | A—Mild (<15% of head affected)
|       | B—Moderate (15–30%)
|       | C—Severe (>30%)
| II    | Lucent and sclerotic changes in femoral head
|       | A—Mild (<15%)
|       | B—Moderate (15–30%)
|       | C—Severe (>30%)
| III   | Subchondral collapse (crescent sign) without flattening
|       | A—Mild (<15% of articular surface)
|       | B—Moderate (15–30%)
|       | C—Severe (>30%)
| IV    | Flattening of femoral head
|       | A—Mild (<15% of surface and <2 mm depression)
|       | B—Moderate (15–30% of surface or 2-4 mm depression)
|       | C—Severe (>30% of surface or >4 mm depression)
| V     | Joint narrowing and/or acetabular changes
|       | A—Mild (average of femoral head involvement)
|       | B—Moderate as determined in stage IV, and
|       | C—Severe estimated acetabular involvement
| VI    | Advanced degenerative changes

*MRI, magnetic resonance imaging.

### Table 15-2: Unified System (Proposed by Enneking)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Event</th>
<th>Criteria*</th>
<th>Quantitation</th>
<th>Location</th>
</tr>
</thead>
</table>
| I     | Infarction/repair | (+) MRI, CT, radiograph | Size of infarct
|       |       |             | A—<15%
|       |       |             | B—15–30%
|       |       |             | C—>30%
| II    | Stalled repair/fracture | (+) CT, radiograph | Length of fracture
|       |       |             | A—<15%
|       |       |             | B—15–30%
|       |       |             | C—>30%
| III   | Deformation | Radiograph | Amount of deformation
|       |       |             | A—<2 mm
|       |       |             | B—2–4 mm
|       |       |             | C—>4 mm
| IV    | Arthritis | Radiograph | Degree of arthritis
|       |       |             | A—Narrowed cartilage
|       |       |             | B—Subchondral sclerosis
|       |       |             | C—Osteophytes

*CT, computed tomography; MRI, magnetic resonance imaging.
vasculature for growth and nutrition, it can be expected that secondary changes will occur in the growth plate after necrosis of the epiphysis. In the early stages of the disease, lytic lesions are often present in the metaphysis, and as a late consequence of cessation of growth, there is widening and shortening of the neck of the femur.

Idiopathic, Nontraumatic or Primary Osteonecrosis of the Femoral Head

Before 1960, aseptic necrosis without a history of fracture was considered unusual. Nowadays, it is recognized to be an important cause of arthritis, a high proportion of the cases being attributable to either treatment with corticosteroids or chronic alcoholism and less commonly to sickle cell disease and Gaucher’s disease.

The most frequent site of clinical subarticular osteonecrosis is the proximal femur commonly seen in men in the fifth decade of life and in women somewhat later. In our own cases, about half of the patients showed radiographic evidence of another site of involvement, either at the time of initial presentation or shortly afterward. The other sites included the opposite hip, the proximal humerus, knee and spine. However the most common site of involvement was the contralateral hip.

Natural History and Diagnosis

In approximately half of the patients, the onset of symptoms is likely to be sudden and acute, although in the rest the onset may be insidious with only vague pain and dysfunction. (The history of acute onset of symptoms is in marked contrast to OA or rheumatoid arthritis, although acute severe and unremitting pain is typical in spontaneous subchondral insufficiency fracture.) However, even in cases in which the onset is insidious, eventually the patient will usually experience a sudden increase in the level and frequency of pain as well as of joint dysfunction. Radiographs taken at this stage often show the crescent sign as already described. Before the appearance of the crescent sign, technetium diphosphonate imaging will generally show a markedly increased uptake of the isotope. MRI is especially helpful in visualizing the bone marrow changes.

In osteonecrosis stages I and II, plain radiographs are generally insufficient for diagnosis and staging, and are diagnostic only in some cases of stage III, in which a characteristic pattern is clearly visible when the hip is correctly positioned. The main advantage of computed tomography (CT) compared with the other imaging modalities is the accurate detection of a subchondral fracture in stage III (Fig. 15-34). The disadvantage of CT is that small lesions might be overlooked.

On bone scintigraphy, a cold spot is a nonspecific pattern and can be found in several other bone marrow processes. The repair process with revascularization, detected as a hot spot, is the most common finding in osteonecrosis but is also nonspecific. Only the combination of a cold and a hot spot represents a diagnostic pattern for osteonecrosis.

MRI is the most accurate imaging modality used for the diagnosis of osteonecrosis of the femoral head, especially in the early stages. Characteristic MRI signal alterations in the anterosuperior portion of the femoral head surrounded by a band of low-signal intensity on T₁- and T₂-weighted images are thought to be diagnostic of osteonecrosis. The occurrence of a double line on the T₂-weighted image is thought to be a pathognomonic sign of osteonecrosis; however, its absence does not eliminate the diagnosis of osteonecrosis. Because the morphologic changes in the necrotic area are mainly the result of the repair process, the MRI scan may show a wide range of more or less inhomogeneous signal alterations.

Diffusely distributed MRI abnormalities, with hypointense signal on T₁-weighted and iso- or hyperintense signal on T₂-weighted images, indicate bone marrow edema and represent a nonspecific pattern seen with several bone pathologies (tumor, infection, insufficiency or stress fracture, and bone marrow edema syndrome or transient osteoporosis).

The limitation of MRI in osteonecrosis is the limited understanding of the histopathologic correlates of the imaging findings with regard to the repair processes. MRI is less sensitive than radiography and especially CT in detecting subchondral fractures or early femoral flattening.
ETIOLOGY OF IDIOPATHIC NECROSIS

Perhaps the most important factors rendering the bone liable to infarction at its articular end are:

- Small diameter of the terminal vessels in the subchondral region
- Lack of a collateral circulation, particularly at the convex surfaces
- Reduced blood flow in the bone which has fatty marrow as compared with that associated with hematopoietic marrow
- Inexpandable nature of the bone tissue.

Necrosis may result from decreased blood flow in the arterial system, due to either narrowing of the lumen, increased viscosity of the blood such as occurs with sickling, embolism, or increased intraosseous pressure obstructing venous outflow.

Increased intraosseous pressure occurs in caisson disease and in replacement of the marrow tissue by an infiltrative process. In the case of patients undergoing cortisone therapy, it has been suggested that there is an increase in the size of the fat cells, which, in turn, result in an increase in intraosseous pressure.

Episodic infarction in patients receiving cortisone therapy has been proposed by Inoue and Ono, who reported that 83% of femoral heads they examined showed histological evidence of recurring necrosis, that is, evidence of death in previously healing areas. However, our own observations have failed to confirm this finding.
Reactive or Post-Traumatic Lesions that may be Mistaken for Malignant Tumors, 362

Florid Reactive Periostitis, 362
Subungual (Dupuytren) Exostosis, 362
Bizarre Parosteal Osteochondromatous Proliferation (Nora’s Lesion), 363

Benign Tumors, 364

Bone Island (Solitary Enostosis), 364
Osteopoikilosis, 364
Melorheostosis, 364

Osteopathia Striata (Voorhoeve’s Disease), 368
Surface Osteomas of the Cranium, Facial Bones, and Other Bones, 368
Osteoid Osteoma, 370
Osteoblastoma, 374

Malignant Tumors, 376

Osteosarcoma (Osteogenic Sarcoma), 376
Paget’s Sarcoma, 386
Radiation Sarcoma, 388
Reactive or Post-Traumatic Lesions that may be Mistaken for Malignant Tumors

Sometimes, the response of tissue to mechanical injury may be mistaken both clinically and pathologically for a malignant neoplasm, and in that regard, some of the problems in the differential diagnosis of stress fractures, as well as traction injuries at various ligamentous insertions, have already been alluded to in Chapter 4. Most pseudosarcomas present on the surface of the bone and are likely to be mistaken for either osteosarcomas or chondrosarcomas. Although various names depending on their location and clinical presentation have been given to the conditions that will be described here, they are certainly all very closely related entities.

FLORID REACTIVE PERIOSTITIS

Florid reactive periostitis is a rare calcifying and ossifying soft tissue lesion that occurs most commonly in the hands and less commonly in the feet. Most of the patients are between 20 and 40 years of age, and women are more commonly affected than men. The condition is usually seen along the margin of one of the short tubular bones, most commonly the proximal and middle phalanges. It is generally believed that the lesion is post-traumatic, although a history of trauma may not be elicited. Imaging studies show that although the lesion appears to arise from the underlying cortical surface, it is without any alteration of the surface architecture of the bone. In the early stages, mineralization may be absent; however, at the time of clinical presentation, calcification is usually present.

Microscopically, especially in the early phases, a disordered loose myxomatous fibroblastic proliferation with large spindle-shaped fibroblasts having prominent nuclei and mitotic activity, together with immature bone and cartilage formation may suggest osteosarcoma (Fig. 16-1). However, as with myositis ossificans, there is usually a zonal arrangement. Local excision may occasionally be followed by recurrence.

FIGURE 16-1 A, Radiograph of a 31-year-old drummer who had had a 5-month history of pain in the little finger. In addition to soft tissue swelling along the ulnar side of the proximal phalanx, there is poorly defined extraosseous calcification. In this case, the differential diagnosis would include myositis ossificans or other reactive lesion, as well as a benign or malignant cartilage lesion. B, Photomicrograph of the tissue obtained from this case of reactive periostitis showing the zoning phenomenon seen at the edge of such lesions. In the upper part of the picture, a loose myxoid tissue gives way to more dense proliferative fibrous tissue. In the lower part of the picture, extracellular matrix is being formed, giving rise to tissue resembling primitive bone or cartilage (H&E, × 4 obj.). (Courtesy of Dr. Leonard Kahn.)

SUBUNGUAL (DUPUYTREN) EXOSTOSIS

Subungual exostosis is a rare osteocartilaginous lesion arising from a distal phalanx, most commonly the big toe. Clinically, the lesion must be differentiated from other subungual lesions that cause ulceration of the nail bed, including verrucae, glomus tumor, epidermal inclusion cyst, subungual melanoma, carcinoma of the nail bed, and pyogenic granuloma.

Most patients are either adolescents or in their early 20s, but occasionally, older individuals might be affected. The symptoms are likely to have been present for a few months, and growth of the lesion may have been rapid. A history of trauma is rarely elicited, although that would seem the most likely cause. However, in a few cases, a recent study has shown rearrangement of the COL12A1 and COLA4S genes.

On imaging studies, the exostosis arises from the dorsal aspect of the tip of the distal phalanx and grows distally. Early in the clinical course of the lesion, it appears as a soft tissue density without attachment to the underlying bone. Later, however, as it calcifies, it begins to show a trabecular pattern and eventually connects to the underlying bone.

The microscopic appearance depends on the stage of maturation. In the early stages, the lesion appears as a focus of proliferating cellular fibrous tissue with areas of cartilaginous metaplasia. Later in its development, it shows focal calcification and ossification mimicking an osteochondroma. However, even in a mature lesion, there is no distinct layer of peristeum covering the cartilage cap, as would be seen with a true osteocartilaginous exostosis (Fig. 16-2); rather the fibrocartilaginous tissue at the periphery of the lesion blends with the overlying fibrous connective tissue. Also in contrast to osteochondroma, the lesion appears to be stuck on to the cortical surface and does not show cortical or medullary continuity with underlying bone. These findings are similar to those of florid reactive periostitis and, like that lesion, may be mistaken for malignancy, especially if biopsy tissue has been obtained only from the periphery of the lesion or early in the course of its development.
The lesion is likely to recur unless it is completely excised, especially if it is removed in the early stages of the disease. (Similar lesions when present in other parts of the phalanges, are often referred to as turret exostoses.)

**BIZARRE PAROSTEAL OSTEochondromATOUS PROLIFERATION (NORA’S LESION)**

Bizarre parosteal osteochondromatous proliferation (BPOP) is a rare aggressive tumorous lesion closely related histologically to reactive periostitis and subungual exostosis. More common in the hands than the feet, they occur most commonly on the proximal or middle phalanges and the metacarpals; they are rarely also seen in the long tubular bones. Usually, there is no history of trauma. Recent studies have strongly indicated that (1;17) (q32;q21) translocations are recurrent and unique aberrations in BPOP.

Problems are most commonly related either to the local mass or to limitation of movement of the nearby joints. Patients are usually young or early middle age, and the sexes are equally affected. Following excision, about 50% recur. Metastasis does not occur.

On imaging studies the lesions may superficially resemble ordinary osteochondromas. However, in contrast to osteochondroma, in which the cortex and the spongiosa of the lesion is continuous with that of the underlying bone, BPOPs arise directly from the cortical surface of the bone and do not show the seamless continuity of lesional and cortical bone characteristic of an osteochondroma.

Microscopically, there usually is a transition, from bizarre fibroblastic proliferation at the periphery to cellular cartilage and disorganized immature bone typically basophilic (blue bone), adjacent to the cortex. Because of its seeming disorganized and cytologic atypia, the lesion may be mistaken for an osteosarcoma or chondrosarcoma. However, like florid reactive periostitis on low-power examination, the lesion generally shows an obvious zonal pattern (Figs. 16-3 and 16-4).

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**FIGURE 16-3**

A, Radiograph of the forefoot of a 28-year-old man reporting pain in the 5th toe. There is a well-defined lobulated and ossified mass in the soft tissue distal to the distal phalanx. This mass does not seem to be attached to the bone of the phalanx. B, A photomicrograph of the resected lesion demonstrates the lobulated cellular cartilaginous tissue and calcified fibrocartilaginous tissue found at the periphery of the lesion. The focal basophilic calcification is a characteristic finding (H&E, × 10 obj.).
Benign Tumors

BONE ISLAND (SOLITARY ENOSTOSIS)

A solitary fleck of increased density in cancellous bone is not an uncommon incidental finding on radiographic images. These foci are found in the intramedullary spongy bone and are composed of compact bone that merges with the surrounding trabecular bone to give a spoke-like pattern at the periphery (Fig. 16-5). Microscopic examination of this tissue reveals mature lamellar bone with well-developed haversian and interstitial lamellar systems (Fig. 16-6). No endochondral ossification or calcified cartilage is observed.

Usually these lesions are only 1 or 2 mm in diameter, but occasionally, they may be as large as 1 cm or even larger. Occasionally scintigraphy may reveal increased uptake of isotope in these lesions, suggesting active growth (Fig. 16-7).

The lesions are probably developmental in origin and significant only in differential diagnosis (e.g., of osteoid osteoma when they are small or of sclerosing osteosarcoma if they are large).

OSTEOPOIKILOSIS

Osteopoikilosis (multiple bone islands) is a rare, symptomless, and clinically benign condition. It is inherited as an autosomal dominant trait characterized by mutations in LEMD3 on chromosome 12q14. On radiographs, the bones show multiple discrete or clustered foci of radiopacity with uniform density, giving the bone a spotted appearance. Usually, the lesions are symmetrical and affect both the epiphyseal and metaphyseal zones. Most commonly, the lesions involve the small bones of the hands and feet, and the ends of the long bones of the extremities. The microscopic features are similar to those of solitary bone islands (Fig. 16-8).

Some cases of osteopoikilosis have been reported in association with cutaneous nodules, which usually prove on microscopic examination to be fibrous tissue resembling scleroderma-like lesions, or keloids (The Buschke-Ollendorff syndrome [BOS]).

MELORHEOSTOSIS

Melorheostosis is a rare, nonfamilial condition related to osteopoikilosis and BOS in having an LEMD3 functional loss mutation. The affected bones display an irregular cortical hyperostosis, similar in appearance to melting wax dripping down the sides of a candle (Fig. 16-9). The lesions occur on both the periosteal and the endosteal surface and may be monostotic, monomelic, or polymelic. Radioisotope bone scans usually show increased uptake in the lesional tissue.
A, Coronal section through an osteoarthritic femoral head reveals a whitish, circumscribed piece of bone, clearly demarcated from the surrounding cancellous bone. B, Radiograph of the specimen illustrated in A demonstrates the marked density of the solitary bone island and its connectedness with the surrounding cancellous bone.

FIGURE 16-5—CONT’D C, A three-dimensional CT reconstruction of the lesion. D, Photomicrograph taken at the periphery of the lesion demonstrates a mixture of bone, fibrous tissue, and calcified cartilage arranged in a bizarre pattern (H&E, × 4 obj.). E, Photomicrograph at a higher power demonstrates the transition of bone and cartilage in this lesion. The bone appears to be benign. The tissue seen here is typical of bizarre parosteal osteochondromatous proliferation (note the presence of “blue bone”) (H&E, × 25 obj.). (Courtesy of Dr. Sharon Wallace, Victoria, Australia.)

A, A bone island consists of dense but normal bone distinctly separated from the surrounding cancellous bone spicules. Note that the spicules merge with the nodule in a radial fashion. The bone is found to be lamellar when viewed under polarized light (H&E, × 1 obj.). B, High-power view of the bone island illustrated in A shows the mature appearance of the bone (H&E, × 4 obj.).
Associated cutaneous lesions, including vascular malformations and focal subcutaneous and para-articular fibrosis, are common, and in children prominent soft tissue fibrosis may predate osseous abnormalities.

With an onset in childhood, the skeleton is characterized by hyperostoses of the bones of the extremities and pelvic girdle, inequality in the length of the extremities, and by contractures resulting in joint deformity. On radiographs, the lesions may be found to involve the epiphysis, and the dense osseous tissue may be seen to cross the growth plate. (Attempts at surgical management of the contractures have been unrewarding.)

With adult onset, the patients most often present with pain, deformity, or limitation of joint motion. The lesion may involve one or many bones. Ectopic bone may be present in para-articular

FIGURE 16-7 A, Anteroposterior radiograph of a knee, showing in the lateral femoral condyle a peripheral island of dense bone delineated by a fine osteolytic rim. B, Scintigram showing increased uptake of ²⁰¹Tc diphosphonate in the lesion. C, Photomicrograph of a section through the lesion demonstrated in A reveals dense cortical bone that merges imperceptibly with the surrounding cancellous bone (H&E, x 1 obj.). (Courtesy of Dr. Leon Sokoloff.)

FIGURE 16-8 A, Radiograph reveals circumscribed dense foci of bone distributed throughout the hand of a patient with osteopoikilosis. B, Nodules of bone with connected spicules of cancellous bone are evident in this photomicrograph of a specimen from a patient with osteopoikilosis (H&E, x 4 obj.).
locations (Fig. 16-10). The involvement of one side of a bone (or row of bones, in some cases) has suggested a sclerotome distribution. On gross examination of the affected bones, the periosteal and endosteal surfaces are irregular, and the bones display thickened cortices. The marrow cavity is narrowed. Histologic examination reveals that the new bone may be either woven or lamellar (Fig. 16-11). However, even when the new bone tissue is lamellar, its cancellous architecture is irregular, and there is a distinct differentiation between the normal and melorheostotic bone.

**FIGURE 16-9** Radiograph of forearm in a 35-year-old man with generalized bone pain and melorheostosis shows the thickened endosteal and periosteal bone that has the characteristic appearance of candle wax dripping.

**FIGURE 16-10** A, Clinical photograph of a female patient with large juxta-articular swellings seen on imaging (B) to be formed of dense osseous tissue.

**FIGURE 16-11** A, Biopsy specimen of cortical bone from a patient with melorheostosis reveals markedly irregular bone with relatively little cellular activity on the endosteal surfaces. The marrow may show mild fibrosis (H&E, × 4 obj.). B, The same histologic field shown in A, photographed with polarized light. Note the irregular mixture of lamellar and woven bone.
OSTEOPATHIA STRIATA (VOORHOEVE’S DISEASE)

Osteopathia striata is a rare benign, asymptomatic disorder characterized radiographically by symmetrical, axially oriented, dense striations in the metaphysis of long bone. Its presence in association with sclerosis of the base of the skull has been determined to be genetically transmitted as an autosomal dominant condition (Fig. 16-12). Osteopathia striata may be seen in association with osteopoikilosis or melorheostosis, or both, in which case the condition is usually referred to as mixed sclerosing bone dystrophy (Fig. 16-13).

SURFACE OSTEOMAS OF THE CRANIUM, FACIAL BONES, AND OTHER BONES

These lesions are relatively uncommon, asymptomatic, benign slow-growing bony tumors usually affecting the calvaria and facial bones. Some osteomas appear on the outer surface of the calvaria as circumscribed, ivory-like excrescences composed of mature lamellar bone (Fig. 16-14). Similar surface osteomas on the long or flat bones are very rare and most likely initially diagnosed as surface osteogenic sarcoma. However, microscopic examination will reveal only mature bone without any associated low-grade fibrous component and usually only nondescript adipose tissue in the marrow spaces (Fig. 16-15).
Osteomas seen on the face are generally associated with the frontal and ethmoid sinuses, and are formed of dense immature woven bone, often with a central area characterized by fibrosis with active osteoblasts and osteoclasts (Fig. 16-16). The etiology of these facial osteomas is obscure; however, microscopically the lesion has a close kinship with osteoblastoma. The lesion does not recur after surgical excision, and it is not associated with malignant change.

Very rarely, this latter type of osteoma is associated with colonic polyps (Gardner’s syndrome). Other disorders characteristically grouped with this syndrome are odontomas, supernumerary and unerupted teeth, and soft tissue tumors, including fibromas and epidermal inclusion cysts.

Gardner’s syndrome is an autosomal dominant genetic disorder, and it is of particular importance because of the malignant change that frequently occurs in the adenomatous intestinal polyps. Gardner’s syndrome is associated with a loss of DNA methylation, which affects a number of cell processes such as gene imprinting. In addition, there are mutations on the APC gene chromosome 5, RAS gene chromosome 18, and TP53 gene chromosome 17.

**FIGURE 16-15** A, Lateral radiograph of the left knee in a 28-year-old obese woman who reported pain in the knee for 2 or 3 months. There is an irregular heavily mineralized mass just above the condyles that is very suggestive of parosteal osteosarcoma. B, A section through the resected specimen shows that the lesion has a dense appearance and is well demarcated from the adjacent cancellous bone. C, Photomicrograph of a typical area of the mass shows compact cortical bone typical of a benign osteoma (H&E, × 4 obj.). D, Polarized light image of the same field shows the mature lamellar bone that makes up the lesion.
Osteoid osteomas are painful lesions of bone that are relatively common, small (less than 1 cm in diameter), solitary, and benign. Characteristically seen in children and adolescents, with boys affected more than twice as frequently as girls (Fig. 16-17), about half the cases present in the lower extremity. The lesions tend to occur near the end of the diaphysis, but almost any bone may be involved and in any location (Figs. 16-18 and 16-19).

The characteristic clinical presentation is nocturnal pain, which is usually relieved by aspirin. On physical examination, local swelling may be apparent and the lesion may be exquisitely tender; mild leukocytosis may be present.

**Figure 16-16**  
A. The protrusion of the right orbit seen in this patient is caused by tumor arising from the bone of the frontal sinus. B. Radiograph demonstrates a well-circumscribed dense lesion that is distorting the frontal sinus (the cause of the orbital protrusion in the clinical photograph). C. Histologic section through the lesion excised from the frontal sinus of the patient shown in A and B. The lesion consists of dense immature bone with a focal area of active bone modeling. Although this lesion is usually referred to as an osteoma, the immature bone and osteoblastoma-like features clearly distinguish it from a routine osteoma (H&E, x 1 obj.). D. Photomicrograph of the more solid area of the lesion to demonstrate the cellular woven character of the bone (H&E, x 10 obj.). E. Photomicrograph to include part of the more active area to demonstrate the fibrous nature of the lesion and the active bone modeling (H&E, x 4 obj.). F. Photomicrograph of a higher power demonstrates active osteoblastic and osteoclastic components (H&E, x 25 obj.).
The typical lesion is located within the cortex of a long bone, and exhibits on imaging studies a central lucent zone (or nidus) with increased sclerosis of the surrounding bone, which may also show marked periosteal new bone formation (Fig. 16-20). (Osteoid osteomas located subperiosteally or in the cancellous portion of the bone may have much less surrounding sclerosis [Fig. 16-21].) On bone scans, the lesions show increased uptake of radioactive isotope. The radiologic differential diagnosis includes a small focus of osteomyelitis or a stress fracture.

When the lesion is close to or within a joint (often the hip), the patient may present with an effusion and symptoms of synovitis.
FIGURE 16-19  A, Low-power photomicrograph of the middle phalanx of a finger. A subperiosteal osteoid osteoma is seen adjacent to the joint margin (H&E, × 1 obj.). B, A specimen photograph of the nidus and surrounding bone. C, Photomicrograph of the curetted tissue reveals woven immature bone with prominent osteoblasts and osteoclasts consistent with an osteoid-osteoma (H&E, × 10 obj.).

FIGURE 16-20  A, A 20-year-old man complained of pain in the midshaft of the right femur. Radiograph shows an area of cortical thickening, in the center of which is a lucent defect that proved on microscopic examination to be the result of an osteoid osteoma. An osteoid osteoma in cortical bone usually produces a considerable amount of reactive bone tissue, as seen in this case. (However, in the cancellous area of the bone, it may be difficult to see the lesion because of a lack of reactive bone sclerosis.) B, Gross photograph of the cortical bone containing the osteoid osteoma. Note the dense center in the nidus and the surrounding hyperemia. C, Radiograph of a slice taken through the nidus shown in B. The nidus is formed of fine bone spicules, and corresponding to the hyperemic zone, a lucent zone lies between the nidus and the surrounding sclerotic cortical bone.
Indeed in such a case, synovial biopsy often reveals a marked lymphoproliferative synovitis. This type of clinical presentation, which is not likely to be immediately diagnosed as osteoid osteoma, is seen in approximately 20% of the cases that are juxta-articular. Osteoid osteomas that are close to the epiphysis may occasionally result in growth disturbance and deformity. Another group of patients in which the diagnosis may be delayed are individuals with lesions in the vertebral column, who might present with scoliosis (Fig. 16-22).

At surgery, the lesion is often difficult to find, although there may be a mild pinkish cast to the overlying cortical bone due to the periosteal reaction and increased vascularity. (Preoperative technetium [99Tc] isotope injection has been used for intraoperative localization of the lesion.) The lesion itself may appear as a well-demarcated nodule, often cherry red (Fig. 16-23), but occasionally very dense and white.

Osteoid osteomas are characterized microscopically by a maze of small spicules of immature bone, most often lined with prominent osteoblasts and increased numbers of osteoclasts (Fig. 16-24). In more mature lesions, the intervening stroma is sparsely cellular, with readily apparent vascular spaces (Fig. 16-25). Cartilage matrix formation does not occur. Very rare cases have been observed in which multiple nidi were present.

A fine grain radiograph may be helpful in determining the location of the nidus of an osteoid osteoma in the curetted tissue submitted at the time of operation for microscopic examination (Fig. 16-26).

The etiology of this bizarre self-limiting condition remains obscure.
Osteoblastoma

An osteoblastoma is a rare solitary, benign, osteoid- and bone-forming neoplasm that contains many well-differentiated osteoblasts and osteoclasts, and usually has a vascular stroma. Osteoblastomas predominantly affect young adults and are often painful. Swelling and tenderness are usually the symptoms that prompt the patient to seek medical attention. In most cases, the long bones or vertebrae are the sites of involvement, with approximately 40% of osteoblastomas originating in the spine. In long bones, the lesion may arise in either the metaphysis or the diaphysis (Fig. 16-27).

In the spine, osteoblastomas arise with about equal frequency in the cervical and lumbar regions, with the thoracic region being less frequently involved (Fig. 16-28). Occasionally, they may involve the pelvis or sacrum. Mainly they affect the vertebral arch, involving the spinous and transverse processes as well as the laminae and pedicles. In only a few cases does the lesion appear to originate within the vertebral bodies. The clinical presentation of osteoblastoma in the spine may include myelopathic or radicular symptoms and often suggests a herniated disc. Progressive scoliosis may also appear and if the cervical spine is affected, reversal of the lordotic curve may occur and torticollis be prominent.

On imaging studies, the lesion characteristically appears as a lucent defect with various degrees of central density. They are usually well circumscribed, without extensive surrounding bone...
sclerosis. They are similar in appearance to ostoid osteoma, with the difference being that the diameter generally exceeds 1.5 cm, and unlike ostoid osteomas, which are self-limiting lesions, osteoblastomas may continue to enlarge. Computed tomography (CT) scanning (Fig. 16-29) and isotope scanning show increased uptake (Fig. 16-30), and both methods are helpful in delineation.

Treatment consists of curettage or en bloc excision. At surgery, an osteoblastoma is found to be composed of hemorrhagic, granular, friable, and calcified tissue (Fig. 16-31).

On microscopic examination, the lesion consists of a vascular spindle cell stroma with abundant irregular spicules of mineralized bone and osteoid (Fig. 16-32). Osteoblasts and multinucleated osteoclasts are readily evident on the bone surfaces. Generally no cartilage can be seen in the lesion; however, in rare cases, foci of cartilage may be found and this in association with focal atypical cells may lead to a misdiagnosis of osteosarcoma.

It is often difficult to differentiate an osteoblastoma from an ostoid osteoma. However, the tissue pattern usually appears less regular in an osteoblastoma than in an ostoid osteoma. Nevertheless, the lesions are similar enough that osteoblastomas have in the past been referred to in the literature as giant ostoid osteomas.

A few patients with either solitary or multiple osteoblastomas have presented with associated weight loss, anemia, and low-grade fever. In these toxic cases, the true diagnosis is apt to be delayed because the patient is usually diagnosed as having osteomyelitis. Curettage of the lesion resolves the toxic symptoms (Fig. 16-33).

On rare occasions, osteoblastomas have been noted to act aggressively, with significant bone destruction and extension into adjacent soft tissues. In these cases, microscopic examination has revealed large, plump osteoblasts that have epithelioid features and may form sheets of cells in the intertrabecular spaces (Fig. 16-34). The nucleoli of these cells may be prominent, and mitoses may be present. In some cases, it may be very difficult to differentiate an aggressive osteoblastoma from a low-grade osteoblastoma-like osteosarcoma. Extremely rare cases of multiple osteoblastomas have been reported, and an example is shown in Figure 16-35.

Changes characteristic of a secondary aneurysmal bone cyst or pathologic fracture may be present within some osteoblastomas, further adding to the problems of differential diagnosis.
Malignant Tumors

OSTEOSARCOMA (OSTEOGENIC SARCOMA)

Osteosarcoma is the second most common primary malignant skeletal neoplasm (myeloma being the most common), and accounts for approximately 20% of all primary malignant bone tumors. It is defined as a malignant neoplasm in which bone matrix is formed by the malignant cells (Fig. 16-36). However, the pluripotential nature of the malignant cells is evident in the abundant fibrous or cartilaginous matrix present in many osteosarcomas.

Roughly 50% of all osteosarcomas are principally osteoblastic; most of the rest are predominantly chondroblastic or fibroblastic; rarely, the tumor may have a small cell– or a giant cell–rich pattern. Occasionally, large areas of the tumor may not be making any discernible extracellular matrix so that histologic diagnosis depends on adequate sampling (Fig. 16-37).

The microscopic heterogeneity of this lesion often leads to confusion with a number of other entities, including fracture callus (especially following a stress fracture without a clinical history of injury), aneurysmal bone cyst, chondrosarcoma, Ewing's tumor, and even giant cell tumor. The diagnostic difficulties may be
Figure 16-30  A slice through an osteoblastoma in the posterior ilium demonstrates the mixed lytic and sclerotic areas that may be seen. (Courtesy of Dr. Alberto G. Ayala.)

Figure 16-31  Radioisotope scan of an osteoblastoma in the transverse process and pedicle of C5. The intense focal uptake is typical of that seen in association with both osteoblastomas and osteoid osteomas. In this case, the size of the lesion indicates that this is an osteoblastoma.

Figure 16-32  A, Photomicrograph of an osteoblastoma shows the usual pattern of disorganized trabeculae of immature bone set in a cellular vascular stroma (H&E, × 2.5 obj.). B, Photomicrograph of an osteoblastoma at a higher magnification shows marked osteoblastic and osteoclastic activity at the bone surfaces (H&E, × 10 obj.).

Figure 16-33  A 16-year-old Indian boy was admitted with hip pain, low-grade fever, and weight loss. A and B, Imaging revealed osteopenia of the right hip and pelvis with a large intrapelvic lesion. A presumptive diagnosis of infection, possibly tuberculosis, was made.

(Continued)
complicated if a pathologic fracture has complicated the underlying lesion (Box 16-1).

In very rare cases, an osteosarcoma may present with more than one focus of tumor. In such a case, it may be difficult to determine whether it is a tumor of multifocal origin or whether the other lesions are metastatic. However, there are some points that suggest a multifocal origin, including symmetrical and simultaneous involvement with metaphyseal lesions in long bones and sparing of the visceral organs.

Most osteosarcomas are high-grade lesions, although less commonly, low-grade osteosarcomas may be encountered, usually as a surface lesion. The discussion that follows will consider

FIGURE 16-33—CONT'D  C and D, Histologic examination revealed a fibrous and osseous tumor classic for osteoblastoma. On removal of the tumor, his initial clinical signs returned to normal and he rapidly regained weight (H&E, C × 10 obj.; D × 25 obj.).

FIGURE 16-34  A to D, Photomicrographs of four separate fields of an atypical osteoblastoma with crowded, large epithelioid stromal cells; small irregular foci of woven bone are present. It is important for the pathologist to recognize that an osteoblastoma may be cellular, and to distinguish this pattern from osteosarcoma, a histologic differentiation that can at times be very difficult (H&E, A and B × 10 obj.; C and D × 25 obj.).
A 40-year-old man was admitted with right foot pain. A and B, Radiographs of the leg revealed multiple well-marginated lytic lesions that were involving the femur, patella, and tibia. The presumptive diagnosis was a vascular tumor. C, A positron emission tomography scan confirmed the presence of multiple lesions including the foot. D to F, Microscopic examination revealed a benign-appearing osseous tumor with the features of an osteoblastoma (H&E, D × 4 obj.; E × 10 obj.; F × 25 obj.).
Bone Tumors

high-grade central lesions (the most common), low-grade central lesions, low-grade surface lesions (so-called parosteal or juxtacortical osteosarcomas), high-grade surface lesions, periosteal osteosarcomas, intracortical osteosarcomas, and finally, sarcomas that complicate Paget’s disease, radiation therapy, and other conditions (Box 16-2).

Central Osteosarcoma, High Grade

Central high-grade osteosarcoma, the most common variant, usually affects children (before the closure of the growth plates) and occurs more often in boys than in girls. About 80% of the lesions occur at the ends of long bones, especially around the knee joint (Fig. 16-38). Localized pain, swelling, and sometimes pathologic fracture present in children who are otherwise in good health. Alkaline phosphatase levels in these patients are generally two to three times normal.
Imaging studies may reveal a sclerotic (in about 35%) (Fig. 16-39), lytic (in about 25%) (Fig. 16-40), or mixed destructive lesion most commonly in the metaphysis; rarely the diaphysis or the epiphysis. In most cases, the tumor has invaded the cortex and extended into the soft tissues at the time of presentation (Fig. 16-41). In many cases, there is abundant periosteal new bone formation (which sometimes shows a ‘sunburst’ pattern) (Fig. 16-42). As with other malignant bone tumors, at the edge of the expansile tumor, elevation of the periosteum may result in a triangle of reactive bone, which is visible on imaging studies and referred to as Codman’s triangle (Fig. 16-43). The sides of the triangle are formed by the periosteum, the underlying cortex, and the narrow margin of the tumor mass. However, the triangle itself is made up of benign reactive bone that may cause diagnostic problems if biopsy specimens are obtained only from this area. Penetration of the tumor into the epiphysis is uncommon and the joint space is rarely involved.
FIGURE 16-43 A, At the upper end of the photograph, a portion of the uninvolved femoral shaft can be seen, whereas at the lower end, the tumor is seen to break through the cortex of the bone. Between the tumor and the normal cortex is a hyperemic zone that has an irregular margin with the cortical bone. This hyperemic zone is composed of reactive bone formed by the periosteum, and would appear on a radiograph as Codman’s triangle. B, A close-up of a slice through the superior anterior aspect of the specimen demonstrates the reactive periosteal bone above and the tumor below. If this reactive periosteal bone is the site of biopsy, it will fail to produce any histologic evidence of malignant tumor. (See also Figure 16-45.)

The gross and microscopic appearance of osteosarcoma varies according to the type of matrix (Figs. 16-44 and 16-45). Most osteosarcomas have in common a pleomorphic and anaplastic cell population that produces an immature and disorganized bone matrix; cartilage matrix or a mainly fibroblastic matrix may be prominent. However, the histologic diagnosis rests on the finding of malignant bone matrix formation (Fig. 16-46). (In this regard, the diagnosis of small cell osteosarcoma is particularly difficult because some patients with Ewing’s tumor that express EWS-Fli-1 and show the typical translocation [11;22] [q24;q12] may produce abundant osteoid, and therefore, the tumors should by definition on morphologic grounds be considered small cell osteosarcomas. In such a case, cytogenetics should take precedence and the tumor classified as being in the Ewing’s family of sarcomas.)

Telangiectatic osteosarcoma is a rare variant of central high-grade osteosarcoma characterized radiographically by a large lytic defect, which is usually expansile and accompanied by an extensive soft tissue component. Magnetic resonance imaging may show fluid levels similar to those seen in an aneurysmal bone cyst (Fig. 16-47). Gross examination reveals a blood-filled cavity; and microscopically dilated vascular channels lined with multinucleated giant cells and an anaplastic sarcomatous stroma with evident bone formation (Fig. 16-48). Occasionally, this lesion may be very difficult to distinguish from an aneurysmal bone cyst.

Osteosarcomas metastasize primarily hematogenously and most commonly to the lungs. Favorable prognostic factors include small or distal lesions. Conventional high-grade central osteosarcoma has no known association with any recurrent genetic alteration; most tumors possess abnormal karyotypes showing multiple structural and numeric chromosome abnormalities. Alterations in the Rb and TP53 pathways are common. Very rarely multicentric osteosarcoma may also on occasion be associated with genetic disturbances as with Rothmund-Thompson syndrome or Bloom’s syndrome (Fig. 16-49).

From the genetic standpoint, there is an interesting association with the inherited form of retinoblastoma. Children with this condition are at high risk for developing a second primary nonocular tumor, notably osteosarcoma. Two genes have been implicated: Rb (on chromosome 13) and p53 (on chromosome 17).

Central Osteosarcoma, Low Grade

Rarely, an intramedullary bone-forming tumor of low-grade malignancy may be encountered. Low-grade central osteosarcoma is usually seen in somewhat older individuals than the conventional high-grade lesion, although individuals in a wide age range may be affected. Men and women are equally affected.

On imaging studies, these lesions are usually either sclerotic, mimicking large bone islands (Fig. 16-50), or resemble foci of solitary fibrous dysplasia (Figs. 16-51 and 16-52), or may be confused with an osteoblastoma. On microscopic examination, they most commonly have a fibrous stroma with rather bland-looking foci of bone formation similar either to the appearance of a conventional surface (parosteal) lesion or mimicking fibrous dysplasia. In other cases, a pattern suggesting osteoblastoma may be seen (Fig. 16-53).
The key to the recognition of these lesions is the identification of the invasive character of the lesion, typified by the presence of islands of residual lamellar bone within the lesion and evidence of malignant tumor bone plastered onto and surrounding these islands of residual bone as shown in Figure 16-51D.

In cases of low-grade central osteosarcomas, the prognosis is generally much better than that of the classic high-grade intramedullary osteosarcoma. However, as with other low-grade sarcomas, dedifferentiation may occur.

**Parosteal Osteosarcoma, Low Grade (Juxtacortical Osteogenic Sarcoma)**

Most commonly, surface osteosarcoma is a low-grade, slow-growing neoplasm that occurs on the external surface of a bone, commonly on the back of the lower end of the femur (the popliteal region) in patients older than 20 years of age (Fig. 16-54). In general, this lesion has a much better prognosis than the classic high-grade intramedullary osteosarcoma. (However, it is important to recognize that some fully malignant osteosarcomas may also present as juxtacortical lesions.)

On imaging studies, the lesion appears as a large, well-circumscribed, generally dense juxtacortical mass, although lytic areas may be present (Fig. 16-55). The mass may be separated from the cortical bone by a fine, relatively lucent line. It is not usually possible to distinguish between high-grade and low-grade surface tumors, and the differential radiologic diagnosis should include that of surface osteoma as well as of a high-grade surface lesion.

Grossly, the tumor is firmly adherent to the bone and, on cut section, may exhibit bony, cartilaginous, and fibrous areas (Fig. 16-56). Microscopically, the lesion consists of a well-defined lobulated
FIGURE 16-45  
A. Gross photograph of a lesion shows a bulky and more vascular osteosarcoma. Extensive soft tissue extension and involvement of the epiphysis may be observed. 
B. Specimen radiograph demonstrates that in the anterior part of the tumor the lesion is purely lytic, that is, without calcified bone formation. Posteriorly, bone formation has occurred, and the newly formed bone spicules are oriented at right angles to the surface of the bone, producing a sunburst pattern. A well-defined Codman’s triangle is apparent at the upper end of the lesion anteriorly. 
C. Low-power photomicrograph of tissue from this tumor shows a cellular pleomorphic tumor that is producing a noncalcified collagenous matrix; focally, this matrix has the appearance of primitive bone (H&E, × 10 obj.).

FIGURE 16-46  
A. Photomicrograph of an intraosseous tumor principally characterized by packed small, round spindled cells, a small cell osteosarcoma. As can be appreciated in this photograph, fine spicules of bone matrix are being formed by the tumor cells in one focus at the left-hand edge of the photograph (H&E, × 25 obj.). 
B. Photomicrograph of a small cell osteosarcoma. Note the regular Ewing-like cells with only small wisps and islands of matrix production (H&E, × 25 obj.).
mass, with extensive bone and (occasionally) cartilage formation. Most tumors contain a bland, well-differentiated fibrosarcomatous stroma (Fig. 16-57).

The treatment of choice is surgical removal of the mass. However, because in many cases intramedullary extension of the lesion has occurred, excision with the attached cortex may not be adequate treatment. Rarely, these lesions may undergo dedifferentiation (Fig. 16-58).

Genetic studies of low-grade parosteal osteosarcoma frequently demonstrate ring chromosomes containing sequences from the long arm of chromosome 12. Amplification of 12q sequences has also been demonstrated in some cases of low-grade central osteosarcoma.

Surface Osteosarcoma, High Grade

It should not be assumed that because a bone-forming lesion has a juxtacortical location it necessarily has a better prognosis. On microscopic examination, the features of a malignant parosteal osteosarcoma are those of a high-grade central lesion. In a high-grade lesion with an intramedullary component, it can sometimes be difficult to decide whether a particular case is a surface lesion or a central lesion with a large soft tissue component.

Periosteal Osteosarcoma

Periosteal (peripheral) osteosarcoma is a rare, predominantly cartilage-forming osteosarcoma characterized on imaging studies by ill-defined swelling and formation of periosteal new bone, which often has a sunburst appearance. The lesion usually occurs at the midshaft of the femur or tibia in children. It is usually small at the time of presentation (Fig. 16-59), although larger lesions may be encountered. The microscopic appearance shows abundant cartilage formation and a cellular stroma (Fig. 16-60). However, malignant bone matrix formation is present and distinguishes the lesion from a juxtacortical chondroma or chondrosarcoma.

Intracortical Osteosarcoma

Cases of osteosarcoma that have an intracortical origin have been only rarely described. One such case of intracortical osteosarcoma is illustrated in Figure 16-61. Intracortical osteosarcomas may be and have been mistaken for an osteoid osteoma.

Treatment of Osteosarcoma

Whereas low-grade osteosarcoma rarely metastasizes and can be treated with surgery alone, high-grade tumors are much more aggressive and regularly spread to lungs. Standard therapy for high-
grade osteosarcoma includes a combination of preoperative neo-
adjuvant chemotherapy followed by limb-sparing surgery when technically feasible. Postchemotherapy resection specimens are rou-
tinely assessed for extent of tumor necrosis because those patients with a good treatment response (90% or greater tumor necrosis) have a superior prognosis.

**PAGET’S SARCOMA**

Rarely, individuals with Paget’s disease, usually advanced polyosto-
tic disease, develop sarcoma. However, on rare occasions sarcoma may occur in patients with nonsymptomatic monostotic disease (for example, in a single vertebral body, see Fig. 7-36). The pre-
senting symptom is likely to be localized pain, which is sometimes associated with a pathologic fracture. Typically the patients are older than 50 years of age. The most common sites are the humerus, femur, and pelvis.

The tumor most frequently associated with Paget’s disease is oste-
osarcoma (Fig. 16-62), although occasionally other patterns of sar-
coma (e.g., chondrosarcoma, malignant fibrous histiocytoma) may be encountered. The prognosis for neoplasms arising in patients with Paget’s disease is poor.

Rarely, a benign giant cell tumor, often in the facial bones, occurs in a patient with Paget’s disease and even metastatic disease or multiple myeloma can occur. For these reasons, it should not be assumed that because a patient with Paget’s disease has evidence of a tumor associated with the disease that the tumor is necessarily a sarcoma (see also Figs. 7-37 and 7-38).
A, A radiograph shows a destructive lesion of the distal end of the proximal phalanx with soft tissue invasion in this adolescent girl with a clinical diagnosis of Rothmund-Thompson syndrome. B, Photomicrograph of the lesional tissue obtained from the lesion demonstrated in A. There are foci of immature bone formation, and the cellular components show pleomorphic nuclei. This was interpreted as osteosarcoma, although there were considerable differences in the expert opinions that were obtained (H&E, × 25 obj.). C, Computerized axial tomogram through the right knee of the same patient. The patella is extremely dense, and an osseous mass is seen in the prepatellar region. The linear defects in the anterior part of the patella represent the area of the biopsy. D, Gross photograph of the articular surface of the patella resected at a later date with surrounding soft tissue. Adjacent to the patella is a tan nodule, which represents part of the soft tissue extension of the patellar tumor. Resection of the tumor was delayed because of differences of opinion in the interpretation of the original biopsy. Resection was performed only after obvious soft tissue extension. E, Photomicrograph of the patellar lesion showing sclerosing osteosarcoma of poor cellularity, which is invading the marrow space and is plastered onto the surface of residual trabecular bone within the medullar cavity (H&E, × 10 obj.).
Section V  Bone Tumors

Bone Tumors

Osteosarcoma, fibrosarcoma, and malignant fibrous histiocytoma are the most commonly diagnosed radiation-induced sarcomas. The tumors present in the radiation field and the most commonly treated lesions that give rise to postirradiation sarcomas are gynecologic cancer and breast cancer (Fig. 16-63). Among primary bone lesions that have been treated by radiation therapy, giant cell tumors seem to be particularly associated with postirradiation sarcoma.

The time interval between radiation and the diagnosis of postirradiation sarcoma may be as long as 40 years, but the average is around 10 to 12 years. Although latencies of 3 years or less are uncommon, the combination of radiation with chemotherapy seems to shorten the interval to sarcoma development. The incidence of sarcomatous degeneration appears to be related to the dose given and the vast majority of cases have received a radiation dose of more than 3000 rad and some much more than that. In general, radiation sarcomas behave in a highly malignant way.

Radiation Sarcoma

Radiation sarcoma

Figure 16-49—cont’d  F. Photomicrograph of the same field shown in E, photographed in polarized light, demonstrates the irregular woven appearance of the collagen matrix produced by the tumor bone. The lamellar pattern of the residual bone is clearly seen.

Figure 16-50 Lateral radiograph of a knee shows a large intramedullary sclerotic lesion that has a spiculated periphery suggestive of a large bone island. On biopsy, this lesion proved to be a low-grade osteosarcoma. (Courtesy of Dr. Lauren Ackerman.)

Figure 16-51 Anteroposterior (A) and lateral (B) views of the leg in a young patient who reported vague pain around the ankle. The radiograph shows an ill-defined sclerotic lesion involving the distal diaphysis and metaphysis of the tibia. The initial impression was that this represented fibrous dysplasia. However, a biopsy proved it to be a low-grade osteosarcoma. C, Gross photograph of a longitudinal section of the tibia in the case illustrated in A and B. There is an intramedullary mass characterized by firm pink-gray tissue, the upper margin of which is well delineated from the bone marrow.

(Continued)
Chapter 16
Bone-Forming Tumors and Tumor-Like Conditions

Figure 16-51—cont’d
D, Photomicrograph of the lesion illustrated in C. The fibrous stroma, although somewhat cellular, has a relatively bland appearance. However, islands of bone are being formed by the tumor, and significantly, this bone is seen surrounding residual trabecular bone. This was a feature of the case and is not seen with fibrous dysplasia. The diagnosis was a low-grade osteosarcoma (H&E, × 4 obj.).

Figure 16-52
Photograph of a low-grade fibrous osteosarcoma in the distal femur. Note the cortex has been eroded and the overlying periosteum is being elevated.

Figure 16-53
A, An anteroposterior radiograph of the pelvis shows a fairly well defined radiodense lesion abutting the sacroiliac joint on the left side. B, A computed tomography scan reveals a bone-forming tumor, which appears in this cut to be confined to the bone C, and this is confirmed by a magnetic resonance imaging scan (MRI). D, In another MRI scan, the tumor is seen pushing the sacroiliac joint, but there is no evidence of extension into the sacrum.

(Continued)
Figure 16-53—cont’d  

E, A photograph of the resected ilium shows the bony nature of the tumor. At the margins, there is slight irregularity as the tumor invades the marrow space (the hole in the tumor is the site of biopsy). 

F, Photomicrograph at low magnification shows a bone-forming tumor with a vascularized cellular fibrous stroma (H&E, × 4 obj.). 

G, The blandness of the tumor is emphasized in this field. However, note the absence of a prominent rim of osteoblasts that is generally seen in an osteoblastoma, which would be the differential diagnosis in this case. Furthermore, there is some atypia and loss of an organized pattern in the fibrous stroma (H&E, × 10 obj.). 

H, Better seen in the somewhat higher magnification (H&E, × 10 obj.). 

I, However, the best evidence of malignancy is the stuccoing of tumor bone on fragments of the normal lamellar bone (H&E, × 4 obj.)
Figure 16-53—cont’d (J), seen here at higher magnification (H&E, x 10 obj.).

Figure 16-54 Location and age distribution of juxtacortical osteosarcoma.

Figure 16-55 A, Lateral radiograph of the knee demonstrates a sclerotic bone-forming tumor involving the lower end of the femur. In this view, it is not possible to determine the involvement of the bone itself. B, Computerized axial tomograms of the lesion shown in A demonstrate that the tumor is entirely confined to the periphery of the bone, with no involvement of the intramedullary bone. (Courtesy of Dr. Leonard Kahn.)
Figure 16-56

A. Gross photograph of the lower end of the femur resected from a patient with a juxtacortical osteosarcoma. A large mass is present on the cortex of the bone just above and between the two femoral condyles. This location is typical for juxtacortical osteosarcoma. B. Gross photograph of a sagittal section through the lesion shown in A demonstrates that the lesion is well encapsulated and formed of bone-producing tissue. As in the case shown here, the lesion frequently extends for a short distance through the cortex into the medullary cavity. For this reason, when surgical treatment of a juxtacortical osteosarcoma is planned, medullary extension should be carefully sought and taken into account if local recurrence is to be prevented. C. Radiograph of the specimen in B. A low-grade juxtacortical osteosarcoma, as shown here, may contain a large area of tumor that is either purely fibrous or cartilaginous, and therefore radiolucent.

Figure 16-57

A. Low-power photomicrograph of a juxtacortical osteosarcoma shows the typical appearance of a heavily collagenized fibrous matrix with irregular trabeculae of bone (H&E, × 4 obj). B. Higher power photomicrograph shows the cellular, though unremarkable, fibrous stroma of a juxtacortical osteosarcoma with islands of bone tissue (H&E, × 25 obj).
FIGURE 16-58 A, A young adult woman reported recent left shoulder pain. A radiograph reveals an extremely dense bone-forming tumor that, although not obvious from this single view, is probably a surface lesion. Additionally there is a destructive lesion affecting the humeral head. B, A section through the resected humerus shows a dense surface lesion and in addition an intramedullary lesion that is destroying the lateral cortex. C, A specimen radiograph clearly distinguishes the dense surface lesion, which has a radiolucent line between much of the tumor and the cortex, and the destructive intramedullary component. D and E, Photomicrographs of the dense osteoblastic surface tumor shows the classic pattern of a low-grade parosteal osteosarcoma.
Figure 16-58—cont’d  F and G, Photomicrographs of the intramedullary portion of the tumor reveals the anaplastic dedifferentiated tumor tissue in the intramedullary cavity. Although uncommon, low-grade osteosarcoma, either on the surface or as a central lesion, may dedifferentiate into a high-grade sarcoma. H, Another field showing cellular anaplastic tumor (H&E, D × 4 obj.; E × 10 obj.; F × 4 obj.; G × 10 obj.; H × 10 obj.).

Figure 16-59 Radiograph of a 14-year-old boy who reported pain in the upper part of the leg. In the proximal tibial diaphysis is a peripheral lesion apparently confined to the surface of the bone. It is composed of an irregular bone-forming lesion, and there is reactive periosteal new bone both superiorly and inferiorly. Histologic examination proved this to be a cartilage-rich periosteal osteosarcoma.
Figure 16-60  A, Anteroposterior radiograph of the lower femur of a 13-year-old girl with a short history of a painless growing mass in the right distal femur. B, Cross-sectional computed tomography scan confirms that this is mainly a surface tumor. C, Gross photograph of a longitudinal section through the lower end of the femur demonstrates a large surface tumor composed of gray-white glistening tissues and admixed bone. D, Radiograph of the dissected specimen demonstrates the extent of bone formation in the tumor. E to G, Microscopic examination reveals a principally cartilaginous malignant tumor with scant bone formation typical of a periosteal osteosarcoma (H&E, E × 4 obj.; F × 10 obj.; G × 25 obj.). (Courtesy of Dr. Leonard Kahn.)
A, A teenage boy reported pain in the shin. The resected specimen demonstrates a tumor confined to the cortical area of the bone. B, A radiograph shows marked cortical thickening with a dense intracortical lesion, which was interpreted as an osteoid osteoma. A biopsy showed an osteosarcoma. C, Histologic section shows an osteosarcoma confined to the cortex of the bone (H&E, × 1 obj.). D, Close-up view of the tumor (H&E, × 25 obj.).
FIGURE 16-62  A, Radiograph of a 65-year-old man, who presented with severe pain in the upper end of the right humerus, shows a large destructive and sclerotic tumor in the upper end of the humerus extending into the soft tissue. Note that the cortex of the bone below the tumor is thickened and indistinct, characteristic of Paget’s disease. B, Sagittal section through the humerus of the patient shown in A shows a large destructive tumor at the upper end. The tumor has extended through the cortex into the soft tissue. (Often, sarcoma in Paget’s disease occurs in the midshaft of the bone, and this finding contrasts with that of primary osteosarcoma, which is more often seen in the metaphysis.) Note the thickened hyperemic cortical bone involved by Paget’s disease. C, Photomicrograph of tissue removed from the patient in B. On the left is pagetoid bone; on the right, a cellular bone-forming tumor (H&E, × 4 obj.).
Figure 16-63  Computerized axial tomogram through the sacroiliac joint of a 52-year-old woman shows an expanding and destructive bone-forming tumor involving the left ala of the sacrum. Biopsy confirmed the diagnosis of sarcoma secondary to previous irradiation of a cervical carcinoma.
**Benign Tumors, 400**

- **Osteochondroma (Osteocartilaginous Exostosis), 400**
- **Multiple Osteochondromas (Hereditary Multiple Osteocartilaginous Exostoses), 402**
- **Dysplasia Epiphysealis Hemimelica (Osteochondroma of the Epiphysis; Trevor’s Disease), 404**
- **Enchondromatosis (Ollier’s Disease), 405**
- **Benign Neoplasms, 405**
  - **Enchondroma, 405**
  - **Juxtacortical Chondroma (Periosteal Chondroma), 408**

**Malignant Neoplasms, 417**

- **Intramedullary Chondrosarcoma, 417**
- **Mesenchymal Chondrosarcoma, 420**
- **Clear Cell Chondrosarcoma, 421**
- **Chordoma, 425**

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**Ernest Amory Codman (1869–1940).** Codman, a native of Boston, was educated at St. Mark’s School, Harvard College, and Harvard Medical School (MD, 1895). An early worker with x-rays, he practiced surgery from 1905 on, specializing in diseases of the bones and joints. He became an authority on bone tumors and diseases of the shoulder, and he later established a registry of bone sarcoma. His book on *The Shoulder*, first published in 1934 is a classic. Codman wrote: “We believe it is the duty of every hospital to establish a follow-up system, so that as far as possible the result of every case will be available at all times for investigation by members of the staff, the trustees, or administration, or by other authorized investigators or statisticians.” (Courtesy of the National Library of Medicine, photograph negative No. 64-73.)

**William Bradley Coley (1862–1936).** Coley was born in Westport, Connecticut, entered Yale College in the fall of 1880, graduated Harvard Medical School in 1888, and was appointed an intern on the surgical service of the New York Hospital. Even at that early date, he showed a keen interest in the subject of sarcoma, following a case that made a very deep impression upon him. This was a four times recurrent, apparently inoperable sarcoma of the neck that had apparently entirely disappeared following an attack of facial erysipelas. After considering experimentation, a preparation consisting of the killed cultures of erysipelas combined with the *Bacillus prodigiosus* was produced, which was found to have a marked inhibitory influence upon certain types of malignant tumors, especially sarcoma. This preparation was known as Coley’s toxin. Most of Dr. Coley’s work with inoperable malignant tumors was carried on at the Memorial Hospital, an institution with which he was connected for more than 40 years. After serving as associate and then attending surgeon at the Hospital for the Ruptured and Crippled, New York, in 1924 Dr. Coley was appointed Surgeon-in-Chief at that institution, a position he held until 1931. (Courtesy of Dr. David Levine.)

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**CHAPTER 17**

**Cartilage-Forming Tumors and Tumor-Like Conditions**
This chapter deals with those benign and malignant tumors in which a cartilaginous extracellular matrix is formed by the neoplastic cells. Occasionally, foci of bone matrix are seen in tumors that are essentially cartilaginous, but in these cases, the bone is reactive rather than having been formed by the neoplastic cells.

**Benign Tumors**

**OSTEOCHONDROMA (OSTEOCARTILAGINOUS EXOSTOSIS)**

Osteochondroma, a cartilage-capped outgrowth from the bone, is a common nonfamilial developmental condition, with the majority of cases presenting clinically in the first 2 decades of life. It is approximately 1.5 times more common in men than in women (Fig. 17-1).

It has been proposed that sporadic osteochondromas result from the herniation and separation of a fragment of epiphyseal growth plate cartilage through the periosteal bone cuff that normally surrounds the growth plate (Fig. 17-2). Persistent growth of the herniated cartilage fragment and its subsequent endochondral ossification result in a cartilage-capped subperiosteal bony projection from the cortex. The most common sites of occurrence are metaphyses of the long bones, usually the lower end of the femur and upper end of the tibia. However, involvement of the flat bones, ilium, and scapulae occurs in about 5% of patients. Osteochondromas of the spine are rare. Rarely, osteochondromas may arise in children following radiation therapy.

On imaging studies, the lesions appear as either a flattened (sessile) or a stalk-like (exostotic) protuberance on the bone shaft in a juxtaepiphyseal location. The bony component is contiguous with the adjacent cortical bone and generally points away from the adjacent joint (Figs. 17-3 to 17-5). On imaging, the stalk merges imperceptibly with the adjacent bone cortex.

**FIGURE 17-1** Location and age distribution of solitary osteocartilaginous exostosis.

**FIGURE 17-2** Histologic section taken from a normal 12-week-old fetus. On the left is the epiphyseal cartilage and the underlying bone metaphysis. To the right of the epiphysis is a thin layer of periosteal bone that forms a cuff around the epiphysis, which is important to the mechanical integrity of the epiphyseal growth plate cartilage during development (H&E, ×40 obj.).
An excised osteochondroma from a child or adolescent is usually an irregular bony mass with a bluish gray cartilaginous cap resembling a cauliflower; the base of the lesion consists of a rim of cortical bone with central cancellous bone. On cut section, the cartilage cap varies in thickness and may show areas with an opaque yellow appearance due to calcification within the cartilage matrix.

On microscopic examination, the cartilaginous cap resembles normal growth plate but has a somewhat disorganized structure.
However, no cellular atypia should be present. The surface is covered with a thin layer of fibrous periosteum (Fig. 17-6). The older the patient, the thinner the cartilaginous cap becomes and after adolescence and closure of the growth plates there is usually no further growth of the osteochondroma. Frequently a bursa forms over the cartilage cap.

The lesion may recur if it is inadequately excised, and this is particularly a problem with sessile lesions in which a part of the cartilage cap may be left behind. In very rare cases, a malignant tumor (usually a chondrosarcoma) may be engrafted onto the lesion.

**Multiple Osteochondromas (Hereditary Multiple Osteocartilaginous Exostoses)**

Cases of multiple osteocartilaginous exostoses are rare (Fig. 17-7). Inherited as an autosomal dominant trait, it is associated with mutations in the exostosin-1 (EXT1) and exostosin-2 (EXT2) genes. If the condition is caused by a mutation in the EXT1 gene, it is called hereditary multiple exostoses type 1. A mutation in the EXT2 gene causes hereditary multiple exostoses type 2. Although both type 1 and type 2 involve multiple exostoses, the severity of symptoms associated with exostoses seems to be greater in type 1. It is estimated that about 15%
A histologic preparation of a pedunculated osteochondroma from a young patient shows a thick proliferating cartilage cap overlying poorly organized cancellous bone. Irregular endochondral ossification is evident at the base of the cartilage cap (H&E, x 1 obj.). B, Low-power magnification of the surface shows the cellularity of the cartilage cap and the covering of periosteum (H&E, x 4 obj.). C, Higher magnification of the cap reveals the disorganized pattern with a vaguely columnar arrangement of chondrocytes similar to that in normal physis (H&E, x 25 obj.). D, Photomicrograph of the cartilage cap at the margin of the exostosis demonstrates the reflected layer of the periosteum over the exostosis, and the irregularity of the chondrocytes within the cartilage cap. Endochondral ossification is apparent at the base of the cap (H&E, x 10 obj.).

Radiograph of an adolescent boy with hereditary multiple exostoses. Note the short, wide, deformed femoral necks, on which can be seen several exostoses. Radiograph of the forearm of the patient shown in A. Note multiple exostoses, with shortening and deformity of the forearm associated with malformation of the distal ulna.
of people with hereditary multiple exostoses have no mutation in either the \textit{EXT1} or the \textit{EXT2} gene. Exostosin proteins are involved in heparin sulfate proteoglycan synthesis, which plays an important role in regulating proliferation at the cartilaginous growth plate.

The patients present with disfigurement or with pain induced by pressure on surrounding soft tissue structures. Individual lesions are similar to solitary osteochondromas on imaging studies, grossly, and microscopically, although usually the multiple lesions are more disorganized in structure and tend to have bosselated cartilage caps.

The significance of this disorder for the surgeon lies in the ongoing management of the multiple lesions; especially because the incidence of malignant transformation, compared with that in solitary osteochondromas, is much higher (about 10%). A lesion with suspected malignant transformation is shown in Figure 17-8.

![Figure 17-8](image)

**FIGURE 17-8** A, This computed tomography scan of the pelvis in a 36-year-old man with known multiple exostoses reveals a large calcified mass on the wing of the ilium, which had been increasing in size. B, Transected specimen removed from the patient shown in A. Note the thick cartilage cap on the surface and the extensive calcification (calcified cartilage) within the irregular bosselated lesion. C, Radiograph of the specimen shown in B again reveals the thick cartilage cap and extensive calcification of the cartilage matrix. D, Photomicrograph of the cartilage cap in the specimen shown in A, B, and C. The cartilage cap is covered with a dense fibrous capsule, seen in the lower right corner, and the cartilage matrix is filled with crowded viable chondrocytes. The finding of a thick, active cartilage cap on an exostosis in a skeletally mature individual (especially if the lesion has a history of recent growth) should alert the clinician and the pathologist to the possibility of malignant transformation [H&E, × 10 obj].

**DYSPLASIA EPiphySEALIS HEMIMELICA (OSTEOCHONDROMA OF THE EPiphYSIS; TREVOR’S DISEASE)**

Dysplasia epiphysealis hemimelica is a nonfamilial developmental disorder of the skeleton, usually manifested in young children who present with unilateral irregular enlargement of an epiphysis (Fig. 17-9). The disorder most commonly involves the epiphyses of the lower femur, the upper tibia, or the talus. Although it is a benign condition, varus or valgus deformities of the limb may develop. Surgical excision is the treatment of choice.

![Figure 17-9](image)

**FIGURE 17-9** Radiograph of a child with an eccentrically enlarged, irregular, capital femoral epiphysis due to an epiphyseal osteochondroma (Trevor’s disease). It is important not to confuse this condition with Legg-Calvé-Perthes disease.
When excised and examined microscopically, the lesion somewhat resembles an osteochondroma, with a cartilage cap of disorganized cartilage, as compared with the surrounding articular cartilage. Underlying the cartilage cap there is endochondral ossification, and normal progression of cancellous bone formation (Fig. 17-10).

ENCHONDROMATOSIS (OLLIER’S DISEASE)

Ollier’s disease is a rare developmental abnormality that appears to have no familial association and is believed to be a random spontaneous mutation. It usually presents in early childhood and is characterized by scattered clones of immature chondrocytes within those parts of the skeleton that develop through the process of endochondral ossification (Fig. 17-11). Characteristically, multiple cartilaginous tumors, either central or subperiosteal, and ranging from microscopic foci to bulky masses, appear throughout the epiphyses, metaphyses, and diaphyses of the affected bones (Fig. 17-12). Their distribution is most often unilateral and confined to one limb.

Imaging studies reveal multiple lucent lesions, often within deformed or shortened bone. A short ulna, as is also seen in association with multiple exostoses, is not uncommon. Stippled calcification within the tumors is common, and occasionally the affected bone may have a striated appearance (Fig. 17-13).

The histologic features of these lesions somewhat resemble those of solitary enchondromas (vide infra), but in enchondromatosis, the tumors are more cellular, frequently myxoid and, in general, have a more ominous appearance (Fig. 17-14). Malignant transformation (rare in solitary enchondromas) is reported to occur in approximately one third of cases and seems to be particularly common in Maffucci’s syndrome, a condition characterized by the occurrence of multiple enchondromatosis in association with soft tissue hemangiomas, including visceral and spindle cell hemangiomas (Fig. 17-15; see also Fig. 21-47).

Benign Neoplasms

ENCHONDROMA

Enchondroma is a relatively common, often asymptomatic, benign intramedullary cartilaginous neoplasm, which most often presents clinically in the short tubular bones of the hands and feet of adults; rarely, they are in the long bones usually as an incidental finding (Fig. 17-16).

When they are in long bones or in the axial skeleton, they may be very difficult to distinguish from low-grade chondrosarcoma. Indeed such differentiation can be among the most difficult problems in bone tumor pathology. However, chondrosarcoma in long bones is more likely to result in pain and on imaging studies to show endosteal scalloping and cortical thickening. On microscopic
examination, invasion of the tumor into the medullary spaces leaving embedded trabecular bone within the tumor is good evidence of malignancy. In general, small peripheral cartilage tumors are usually benign, whereas large axial tumors are more likely to be malignant.

In short tubular bones, an enlarging lesion may fracture, and this complication is a common reason for clinical presentation. Rarely, an eccentric chondroma may cause bulging of the cortex. (This appearance has been referred to as enchondroma protuberans.)

On imaging studies enchondroma usually appears as a well-delineated solitary lucent defect in the metaphyseal region of the bone and in the small tubular bones, most of the shaft is usually involved. The cortex is generally intact unless a fracture through the weakened bone has occurred (Fig. 17-17). Calcification is usually present in the lesion, appearing as fine, punctate stippling or small broken rings of radiodensity (Fig. 17-18). In long bones, when calcification is pronounced, the radiograph may be suggestive of a bone infarct; however, in general, a bone infarct shows peripheral calcification that more resembles a coil of smoke.
Figure 17-14  

A, Low-power photomicrograph of the articular end of a bone from a patient with multiple enchondromatosis demonstrates a cartilaginous nodule extending up to the articular surface. Note the lobular arrangement of the cartilage and the lesion’s bony rim (H&E, × 1 obj.).  

B, Photomicrograph of a portion of the lesion shown in A demonstrates the lobular and cellular appearance of the cartilaginous nodules in enchondromatosis. These lesions usually exhibit more cellularity than is seen in solitary enchondromas (H&E, × 10 obj.).  

C, Higher power view shows the myxoid appearance of the tumor with crowded stellate cells (H&E, × 25 obj.).

Figure 17-15  

A, Radiograph of a hand in a patient with multiple enchondromas reveals many calcified phleboliths in association with soft tissue hemangiomas. This combination of soft tissue hemangiomatosis and enchondromatosis is known as Maffucci’s syndrome.  

B, In the right femur of this patient with Maffucci’s syndrome, a large chondrosarcoma has developed.
Gross examination of an enchondroma in situ reveals bluish gray lobules of firm, translucent tissue. On microscopic examination, these lobules are composed of proliferating nests of cartilage cells without obvious atypia. Foci of calcification are usually present, and a thin layer of lamellar bone rimming the cartilage nodules is sometimes observed. Occasionally, evidence of endochondral ossification is seen. Invasive infiltration of the bone marrow spaces is not a characteristic of benign enchondromas, and this is probably the most helpful microscopic feature in distinguishing an enchondroma from a low-grade chondrosarcoma.

Rarely, a chondrosarcoma develops in a pre-existing enchondroma, usually in long tubular bones (Fig. 17-19).

The examination of cross-sections of a large number of surgically removed femoral heads in our experience occasionally reveals small nodules of cartilage, which are usually less than 1 cm in diameter. Such nodules are perhaps best regarded as benign cartilage rests (Figs. 17-20 and 17-21).

**JUXTACORTICAL CHONDROMA (PERIOSTEAL CHONDROMA)**

Juxtacortical chondroma is a benign cartilaginous lesion characterized by its location on the metaphyseal cortex of both long and short tubular bones. On imaging studies, a cup-shaped or scalloped cortical defect with a sclerotic margin is usually evident; the lesion, which is rarely more than 3 to 4 cm in diameter, typically has overhanging edges (Fig. 17-22). On gross inspection, juxtacortical chondroma is a well-circumscribed lesion that is partially embedded in cortical bone and covered by the periosteum. Its cut surface is grayish white or bluish and lobulated. When examined microscopically, the proliferating chondrocytes show minimal pleomorphism and nuclear abnormalities. Although limited extension into adjacent cortex may be seen, penetration through cortex into medullary cavity suggests a juxtacortical chondrosarcoma. Focal calcification and ossification may occur within the cartilage (Fig. 17-23).

The treatment of a juxtacortical chondroma is en bloc resection.

**CHONDROBLASTOMA**

Chondroblastoma is an uncommon, benign cellular calcifying giant cell neoplasm most often located in the epiphysis of long bones, and usually diagnosed in the patient’s second decade of life.
Figure 17-18 Anteroposterior (A) and lateral (B) radiographs of a 52-year-old man with pain in the knee joint show a heavily calcified intramedullary lesion in the lower end of the femur. There were no apparent symptoms related to this lesion. Histologic examination revealed a heavily calcified cartilage tumor, interpreted as an enchondroma. C, Photomicrograph of the lesion shown in A and B reveals a calcified cartilaginous lesion. The cartilage cells are uncrowded and unremarkable (H&E, × 10 obj.). D, Frequently in enchondroma, the cartilage lobules are surrounded by a narrow rim of bone, as shown in this photomicrograph (H&E, × 25 obj.). E, In this specimen radiograph of an enchondroma of the distal fibula, the typical radiographic features of an enchondroma are well illustrated.
The characteristic findings on imaging studies include a well-demarcated, often lobulated lucent defect with mottled calcification, located in the epiphysis and sometimes extending into the metaphysis of long bones (Figs. 17-24 and 17-25). The cortical bone may be intact or expanded. The lesion has a predilection for the upper end of the humerus, the upper and lower ends of the femur, and the upper end of the tibia, and in most cases the diagnosis can be made with some confidence from the radiographs because of the characteristic location and the patient's age. Magnetic resonance imaging (MRI) studies characteristically show low signal intensity on T2 images with high signal in surrounding marrow cavity and adjacent soft tissue, which correlates with associated edema. On rare occasions these lesions may occur in older individuals and in odd locations, such as the spine or a flat bone (Fig. 17-26).

FIGURE 17-19 Photomicrograph demonstrates the development of a chondrosarcoma in a patient with pre-existing enchondroma. In the upper center part of the photomicrograph, a heavily calcified enchondroma is apparent. In the left and right parts, a cellular myxoid chondrosarcoma is present (H&E, × 4 obj.).

The characteristic findings on imaging studies include a well-demarcated, often lobulated lucent defect with mottled calcification, located in the epiphysis and sometimes extending into the metaphysis of long bones (Figs. 17-24 and 17-25). The cortical bone may be intact or expanded. The lesion has a predilection for the upper end of the humerus, the upper and lower ends of the femur, and the upper end of the tibia, and in most cases the diagnosis can be made with some confidence from the radiographs because of the characteristic location and the patient's age. Magnetic resonance imaging (MRI) studies characteristically show low signal intensity on T2 images with high signal in surrounding marrow cavity and adjacent soft tissue, which correlates with associated edema. On rare occasions these lesions may occur in older individuals and in odd locations, such as the spine or a flat bone (Fig. 17-26).

FIGURE 17-20 Gross photograph of a femoral head resected for osteoarthritis. A small cartilage rest is present in the neck of the femur. Note the glistening, lobulated, bluish white appearance of the cartilaginous tissue.

FIGURE 17-21 A, Photomicrograph of a section through a femoral head that contains a large multilobular cartilage rest (H&E, × 1 obj.). B, A specimen radiograph of the lesion. C, Photomicrograph of the lesion (H&E, × 4 obj.).
FIGURE 17-22  A, Anteroposterior and lateral radiographs of the lower femur of a young girl with a palpable mass behind the knee. After resection, this proved to be a large juxtacortical chondroma. B, Another juxtacortical chondroma at the upper end of the humerus seen in a cross-sectional computed tomography scan.

FIGURE 17-23  A, Radiograph of a hand shows a well-defined saucer-like depression of the cortex at the proximal end of one phalanx. This radiographic picture is typical of a juxtacortical chondroma. B, Photomicrograph of the lesion illustrated in A shows a cellular and focally calcified benign cartilaginous lesion (H&E, × 4 obj.). C, Higher magnification of B shows mild to moderate atypia (H&E, × 25 obj.).
Curettage generally produces a gritty, grayish pink tissue (Fig. 17-27) that is characterized microscopically by round and ovoid cells with a modest amount of eosinophilic cytoplasm and frequent nuclear grooves, which are S-100 protein positive, these cells are mixed with varying numbers of scattered giant cells. Focally, an intercellular chondroid matrix is produced in which a lace-like deposit of calcium granules is typically observed (so-called chicken-wire calcification) (Figs. 17-28 to 17-30). In contrast to most hyaline cartilaginous lesions, the cartilaginous matrix in chondroblastoma is frequently eosinophilic. The presence of cartilage and giant cells in chondroblastomas may on occasion lead to diagnostic confusion of the lesion with either chondrosarcoma or giant-cell tumors of bone.

In about 20% of cases, the lesions are cystic and hemorrhagic (cystic chondroblastoma). Because the majority of the lesion may be cystic, inadequate sampling may give rise to a diagnosis of aneurysmal bone cyst. Whereas in typical cases of chondroblastoma the S-100 protein is strongly positive in the mononuclear cells though...
negative in the giant cells, in the presence of cystic changes, the S-100 protein may be only focally positive.

Curettage or local excision is the treatment of choice. In very rare cases, soft tissue implants or lung metastases may occur; when present, they are usually rimmed with bone (Fig. 17-31). These implants or metastases should be surgically removed.

CHONDROMYXOID FIBROMA

Chondromyxoid fibroma is a very rare, benign bone neoplasm most often discovered during the patient’s second or third decade of life. The lesion usually occurs eccentrically in the metaphysis of the lower femur or upper tibia, or in the short tubular bones of the foot,

FIGURE 17-27 Photograph of a curetted chondroblastoma. Note the granular appearance and the clearly yellow calcified areas. (Courtesy of Dr. Miguel Calvo.)

FIGURE 17-28 Photomicrograph of a chondroblastoma demonstrates the varied appearance of this lesion. Cellular areas mixed with areas of cartilage matrix formation and calcification can be seen (H&E, × 10 obj.).

FIGURE 17-29 A, Photomicrograph reveals the juxtaposition of an area of chondroid matrix on the lower left, with a more cellular area of polyhedral cells and admixed giant cells on the upper right (note the eosinophilia of chondroid matrix) (H&E, × 4 obj.). B, Photomicrograph shows a higher magnification of a cellular area (H&E, × 25 obj.) and C of the matrix producing area (H&E, × 25 obj.).
but it may occasionally develop in other bones (Fig. 17-32). Patients usually present with pain or local swelling.

On imaging studies, the lesion is characterized by an eccentric well-demarcated lucent defect with a thin, well-defined scalloped border of sclerotic bone (Figs. 17-33 and 17-34). (When imaging any cartilage-containing lesion, the bright signal that characterizes the $T_2$ image on MRI helps to differentiate these lesions from fibrous or cellular lesions.)

Inspection of intact gross specimens shows that the lesion is usually sharply demarcated and covered on its outer surface with a thin rim of bone or periosteum. Examination of the cut surface demonstrates a firm, lobulated, grayish white mass, sometimes with small cystic foci and areas of hemorrhage.

On microscopic examination, chondromyxoid fibroma has a lobulated pattern, with sparsely cellular lobules alternating with more cellular zones. The sparsely cellular lobules show spindle and stellate cells without distinct cytoplasmic borders in a myxoid or chondroid matrix. Running between the lobules are fibroblastic septae of increased

**Figure 17-30** Fine stippled calcification is characteristic of chondroblastoma and frequently extends around the individual chondroblasts, producing a chicken-wire appearance (H&E, × 25 obj).

**Figure 17-31** Lateral radiograph of the knee of a young adult man who, 18 months before, had had a transarticular curettage of a chondroblastoma of the lower femur. There are now three implanted nodules, which proved to be chondroblastoma in the popliteal space; each is surrounded by a rim of bone.

**Figure 17-32** Location and age distribution of chondromyxoid fibroma.
cellularity, with scattered multinucleated giant cells. Some nuclear pleomorphism may be evident, but mitotic figures are rare (Fig. 17-35).

Because recurrence of the lesion after curettage is frequent, en bloc excision is the preferred treatment.

The cells in the myxoid areas generally are weakly positive for S-100 protein.

**Figure 17-33** Radiograph of the elbow joint in a young adult man who complained of pain shows a well defined, trabeculated lytic lesion with cortical thinning but no obvious soft tissue extension. This soap bubble appearance is typical of chondromyxoid fibromas, although these lesions are so rare that the diagnosis is usually not made until after histologic examination.

**Figure 17-34** Computed axial tomogram through the lumbar region of a young woman who presented clinically with weakness in the right leg. It shows an expanded lesion involving both the posterior elements and the vertebral body. On biopsy, this lesion proved to be a chondromyxoid fibroma. (Courtesy of Dr. Julius Smith.)

**Figure 17-35** A. Gross photograph of a segment of resected fibula with a chondromyxoid fibroma. Note the well-demarcated lesion and the glistening fleshy appearance. B. Photomicrograph of a chondromyxoid fibroma shows the typical lobulated and variegated appearance of this lesion. Lobules of chondromyxoid tissue and septa of cellular fibrous tissue are evident, with occasional multinucleated giant cells running between the lobules (H&E, × 10 obj.).
Fibromyxoma is microscopically superficially similar to a chondromyxoid fibroma (and may represent a variant of chondromyxoid fibroma), but it is even more rare and occurs in older individuals. Fibromyxoma lacks both the lobular pattern and the chondroid matrix that typify a chondromyxoid fibroma.

The lesion is so rare that no radiographic characteristics have been substantiated. The radiograph shown in Figure 17-36 was thought to be of a giant cell tumor. However, histologic examination showed it to be of a fibromyxoma. Follow-up of the few cases described in the literature has revealed no instances of local recurrence or metastases.
Chondrosarcoma is a malignant neoplasm with cells that produce cartilage matrix. Bone matrix made by the malignant cells is not present in chondrosarcoma, although on occasion there may be foci of benign reactive bone. Characteristically seen in adults in the fifth and sixth decades of life (Fig. 17-37), it occurs most frequently in the pelvis and in the medullary cavity of the femur, humerus, and ribs (Figs. 17-38 and 17-39). Patients initially complain of persistent mild pain and often of local swelling.

On imaging studies, chondrosarcomas in the long bones are located in the metaphysis and often extend into the diaphysis to produce a fusiform, lucent defect with a scalloped inner cortex. Thickening and inequality of the cortex are common radiographic findings and, when associated with pain, help to distinguish a chondrosarcoma from an enchondroma. Extension into the soft tissue should be looked for. Frequent punctate or stippled calcifications are characteristic (Fig. 17-40). Occasionally, extensive calcification may give rise to the radiologic confusion of chondrosarcoma with a bone infarct. MRI will show a characteristic bright signal on T2 images and is most helpful in showing the extent of the tumor.

Grossly, chondrosarcomas are lobulated, grayish white or blue, focally calcified masses, often with areas of mucoid degeneration or necrosis.

Microscopically chondrosarcoma are graded into three groups:

1. Grade I: low-grade chondrosarcomas are cytologically so similar to enchondromas that the diagnosis is mostly dependent on the clinical and radiologic presentation, and on the location. Pain, cortical thickening, and possible soft tissue extension are important findings. Those lesions located in the pelvis, scapula, or ribs in general behave more aggressively than those in long bones. Microscopic evidence of invasion of the haversian canals or of the medullary space with embedded fragments of trabecular bone within the tumor are the most helpful findings in making the distinction from a benign enchondroma (Fig. 17-41).

2. Grade II chondrosarcoma shows a definite increased cellularity with increased nuclear size and distinct nucleoli in many of the cells. Binucleate cells are common. Focal myxoid change is a frequent occurrence, and predominantly myxoid chondrosarcomas are generally assigned grade II (Figs. 17-42 and 17-43).
3. Grade III: high-grade chondrosarcomas are comparatively rare. They are characterized by marked cellular atypia, hypercellularity, and high mitotic activity. They are generally rapidly growing, aggressive, and frequently metastasize. They have an aneuploid pattern on flow cytometry and show complex aberrations on chromosomal analysis (Fig. 17-44).

It is generally true that lesions in the axial skeleton and proximal portions of the appendicular skeleton are more likely to pursue a malignant course than tumors in the distal skeleton. (However, it is important to recognize that on rare occasions, chondrosarcomas may arise in the digits [Fig. 17-45].) Furthermore, infiltration of the marrow spaces occurs in chondrosarcomas, so that trabeculae of

FIGURE 17-39 A, In this radiograph, a large calcified mass is present adjacent to the lumbar spine. This lesion proved to be a low-grade chondrosarcoma. B, Gross photograph of the lesion. C, Radiograph of the specimen shown in B demonstrates irregular areas of calcification.

FIGURE 17-40 A, A 42-year-old man with a swelling on the anterior left 4th rib. B, Computed tomography scan showing an enlarging lesion at the costochondral junction.
normal bone may be found embedded in the tumor. In assessment of low-grade chondrosarcomas, this microscopic finding is the most helpful feature in distinguishing the lesion from an enchondroma (Fig. 17-46).

The clinical course of chondrosarcoma depends on several factors. In general, well-differentiated tumors rarely metastasize, but they recur locally after incomplete excision. Anaplastic, fully malignant tumors metastasize early, primarily to the lung. Grade II chondrosarcoma may metastasize in about 10% to 15% of cases. Complete surgical excision of the tumor is the treatment of choice. (Cartilage lesions do not usually respond well to chemotherapy or radiation therapy.)

About 10% of all chondrosarcomas undergo dedifferentiation and become highly malignant sarcomas with spindle cells and bizarre giant cells (features of fibrosarcoma or malignant fibrous histiocytoma [Fig. 17-47]). These dedifferentiated tumors carry a
poor prognosis and often metastasize widely, the metastases frequently showing only the spindle-cell component of the tumor. Images in such a case may reveal a poorly defined and destructive lucent zone in an otherwise typical chondrosarcoma with stippled calcification.

MESENCHYMAL CHONDROSARCOMA

Mesenchymal chondrosarcoma is a rare, malignant bone tumor that has been seen most commonly in individuals in the second and third decades of life. Almost any bone may be affected, although there is a reported predilection for the maxilla, mandible, and ribs. Approximately one third of the lesions have been found in soft tissue. Patients may experience pain and/or swelling.

An ill-defined osteolytic lesion with irregular calcifications may be noted on imaging studies, and this appearance corresponds to the grayish white or yellow tumor mass, sometimes with evident foci of cartilage and calcification on gross examination. On microscopic examination, the characteristic feature of these lesions is a biphasic pattern. The majority of the tumor is composed of small, uniform, round- to spindle-shaped cells with a perivascular arrangement of cells that may result in a hemangiopericytoma-like pattern.
Within this cellular component, there are focal admixed areas of a cartilaginous or chondroid matrix arranged in a lobular pattern (Fig. 17-48). S-100 protein is found only in the cartilaginous components of the tumor. Two cases of mesenchymal chondrosarcoma have shown an identical Robertsonian translocation resulting in a derivative chromosome der(13;21) (q10; q10).

Mesenchymal chondrosarcoma metastasizes primarily to the lungs, but osseous and soft tissue metastases have been documented.

**CLEAR CELL CHONDROSARCOMA**

Clear cell chondrosarcoma, the least common variant of chondrosarcoma (considered by some to possibly represent an aggressive variant of chondroblastoma), is a destructive low-grade malignant tumor that presents most commonly in young adults, predominantly men.
**FIGURE 17-48**  
A. Clinical radiograph of a young man who presented with leg pain and swelling. A soft tissue mass is eroding the adjacent bone between the fibula and the tibia. Focal calcification is evident within the tumor mass. In this case, the differential diagnosis would have to include synovial sarcoma.  
B. Gross photograph of the resected specimen from the patient in A shows a soft tissue tumor eroding the cortex of the adjacent fibula.

**FIGURE 17-47—CONT'D**  
B. Specimen radiograph of the dedifferentiated chondrosarcoma shown in A. Although the cartilaginous portion of the tumor is heavily calcified, the dedifferentiated spindle cell component is entirely radiolucent.  
C. Photomicrograph of the dedifferentiated spindle cell tumor that developed in the chondrosarcoma illustrated in (A) and (B). The spindle cell tumor has the pattern of a malignant fibrous histiocytoma and is seen here abutting the chondrosarcoma (H&E, × 10 obj).
FIGURE 17-48—CONT’D  

C, Specimen radiograph of the lesion shown in B. Focal calcification is seen, particularly at the periphery of the lesion.  
D, Photomicrograph of a portion of a mesenchymal chondrosarcoma showing nodules of cellular chondroid tissue on either side and between a vascular cellular tumor (H&E, × 4 obj.).  
E, Higher power photomicrograph of the cellular vascular component shown in D. Note the small closely packed spindle cells surrounding the vascular spaces and resembling the pattern of a hemangiopericytoma (H&E, × 40 obj.). (D and E courtesy of Dr. Andrea Deyrup.)

FIGURE 17-49  

A, Radiograph of wrist in a 59-year-old man. The destructive lesion in the distal ulna turned out to be a clear cell chondrosarcoma, although that was not part of the differential diagnosis.  
B, Photomicrograph of the lesion shows the classic pattern of packed chondrocytic cells with vacuolated cytoplasm (H&E, × 10 obj.).  
C, S-100 positivity in the vacuolated tumor cells (× 10 obj.).
It was originally thought to affect only the epiphyseal ends of long bones, most often the upper femur. However, as these lesions have become more commonly recognized, it has become clear that by no means are all clear cell chondrosarcomas located in the epiphysis or in the upper femur.

On imaging studies, these tumors are well-circumscribed mixed lucent and sclerotic defects, often with a thin sclerotic border (Figs. 17-49 and 17-50) and scattered calcification. When located in the epiphysis, they are most likely to be diagnosed radiologically as chondroblastoma or giant cell tumor.
On histologic examination, a clear cell chondrosarcoma contains many cells with abundant clear or palely eosinophilic, vacuolated cytoplasm rich in periodic acid–Schiff (PAS)–positive glycogen, which often lie between heavily calcified cartilage matrix and woven bone. Frequently, scattered giant cells are present (Fig. 17-51). The vacuolated clear cells may suggest renal cell carcinoma, but the scattered giant cells and the scant chondroid matrix should help to differentiate the two lesions. The cells of clear cell chondrosarcoma are strongly positive for S-100 protein.

Clear cell chondrosarcomas may be indolent but can be locally aggressive; metastases have been reported.

CHORDOMA

Although chordoma may have a superficial similarity to a cartilage lesion, it is a neoplasm that arises from remnants of the notochord, and therefore, in almost all cases, it occurs in the midline of the axial skeleton. About half the cases occur in the sacrococcygeal region, whereas one third are present at the base of the skull. The remaining cases arise at different sites along the vertebral column, most commonly in the cervical region. Chordoma is a slow-growing neoplasm, causing clinical symptoms that depend on its location. (Cranial lesions usually are smaller than sacrococcygeal lesions at the time of initial presentation.) Men are more frequently affected than women; the average age at diagnosis for sacral lesions is approximately 55 years and, for sphenoid-occipital lesions, somewhat younger (Fig. 17-52).

On imaging studies, bone destruction is the hallmark of chordoma, and about half of the patients exhibit focal calcifications within the lesion (Fig. 17-53). Localization of the lesion has been greatly aided by the use of MRI, particularly in cases of intracranial chordoma (Fig. 17-54). When chordomas affect areas of the spine other than the two common sites (i.e., sacrococcygeal and cervical), the lesions are likely to be lytic, located centrally within the vertebral body, and slowly expansile. When the cervical vertebrae are affected, extension anteriorly into the soft tissues may result in dysphagia (Fig. 17-55), whereas posterior extension may lead to neurologic complications. Since giant notochordal rests may also occur within the vertebral bodies, they need to be differentiated from chordoma (vide infra). Systemic metastases to the regional lymph nodes, lung, liver, and bone occur in up to 25% of cases.

On gross examination, chordomas are generally soft and appear to be well encapsulated. Lobulations are apparent on cut section, and the tumor usually has a bluish gray color with extensive gelatinous translucent areas that are focally cystic and hemorrhagic (Fig. 17-56). Grossly, the tissue may suggest a chondrosarcoma or even a mucinous carcinoma.

Microscopic examination reveals a characteristic arrangement of tumor cells separated into lobules by fibrous septa of different thicknesses. The tumor cells are of various sizes and shapes, arranged in both cords and sheets, with an eosinophilic cytoplasm associated with both extracellular and intracellular mucin that may be minimal or abundant. The intracellular vacuoles may be very prominent and displace the nucleus to one edge, producing the
so-called physaliphorous cell (Fig. 17-57). The tumor cells express both S-100 protein and epithelial markers.

Approximately one third of sphen-occipital chordomas contain a significant chondroid component, and these lesions can easily be confused with chondrosarcomas, especially with chondrosarcomas having a predominantly myxoid structure (Fig. 17-58). Rarely, an associated malignant mesenchymal tumor has been described in association with a chordoma, either a malignant fibrous histiocytoma or another poorly differentiated sarcoma (i.e., dedifferentiated chordoma); at least some of these cases have been associated with a history of radiation therapy.

On occasion, a large notochordal rest in a vertebral body may be discovered as an incidental finding on MRI. In such a case, the differentiation from a chordoma may be a problem, although in a chordoma, there is generally a lytic lesion seen on radiographic imaging, whereas this has not been the case with the notochordal rests, which have been reported to be more often associated with bony sclerosis. Microscopically, notochordal rests lack myxoid extracellular material and their close resemblance to marrow fat makes them easy to overlook. Reactive bony sclerosis is often evident, and the lesions do not show extraosseous extension (Fig. 17-59). Immunostains for cytokeratin and S-100 label the lesional cells.

FIGURE 17-53 Radiograph of a 60-year-old man, who reported pain in the coccygeal region, reveals destruction of the sacrum and the coccyx by a large, lytic, expansile lesion, which on biopsy proved to be a chordoma.

FIGURE 17-54 A sagittal spin-echo magnetic resonance imaging scan shows a large chordoma filling the nasal cavity and ethmoid sinus anteriorly. It has obliterated the nasopharynx, extending inferiorly into the hypopharynx. Rostral to the odontoid process, it extends into the cranial cavity, completely destroying the clivus. It has invaded or displaced the brain stem, extending directly to the anterior aspect of the fourth ventricle.

FIGURE 17-55 Lateral radiograph of a 40-year-old man who presented with dysphagia and myelopathy. There is a destructive lesion involving C3 and C4, with an anterior soft tissue extension that partially occludes the airway, which proved to be a chordoma.
Figure 17-56  
**A.** Photograph of a sagittal section obtained at autopsy through the lower lumbar spine and sacrum of a patient with chordoma. The tumor has largely destroyed the sacrum and is involving L5. A large anterior component is present. The tumor tissue shows a characteristic lobulated, firm blue gray tissue mass, with focal hemorrhage and cystification.  
**B.** Photomicrograph shows the nests and cords of tumor cells with abundant eosinophilic cytoplasm separated by lakes of mucoid tissue (H&E, × 10 obj.). (A courtesy of Dr. Mario Campanacci.)

Figure 17-57  
**A.** In some areas of chordoma, large mucoid foci are present; in these mucoid areas, cords of eosinophilic cells may be present (as in this photomicrograph) (H&E, × 40 obj.).  
**B.** Photomicrograph shows the large variegated and vacuolated cells characteristic of chordoma (physaliphorous cells) (H&E, × 40 obj.).
In some patients with chordomas arising in the area of the clivus, the tumor has a distinctly chondroid appearance (as in this photomicrograph). This chondroid pattern is important to recognize, because the prognosis for patients with chondroid chordomas in the base of the skull is believed to be better than for patients with a conventional pattern of chordoma in that area (H&E, × 10 obj).

A

Magnetic resonance T1-weighted image demonstrating a large defect in the body of L3 that was not visible on the plain radiograph.

B

A biopsy reveals tissue consistent with giant notochordal rest. Lesional cells resemble mature fat and lack cytologic atypia. In contrast to conventional chordoma, no myxoid extracellular material is seen (S-100– and cytokeratin-positive). (A courtesy of Dr. German Steiner; B courtesy of Dr. Mark Edgar.)
Lauren Vedder Ackerman (March 12, 1905 – July 27, 1993). Born in Auburn, New York, Ackerman received his MD from the University of Rochester, NY. After completing his training in internal medicine at the University of California at San Francisco, he proceeded to a pathology residency in Massachusetts, where he worked with Shields Warren, developing there a lifelong interest in tumor pathology. Ackerman is regarded as the father of surgical pathology in the United States, and as Professor and Director of the Laboratory of Surgical Pathology at Washington University, he trained many who later became leaders in the field. As one of the founding members of the New York Bone Club in 1978, he is seen (right) in this photograph with the author (left), pursuing another of his lifelong interests. (From the author’s collection.)

David C. Dahlin (1917–2003). Dahlin was born in a small town in South Dakota. He completed his premedical studies at the University of South Dakota and was admitted to Rush Medical School in Chicago at the age of 21 years. Dr. Dahlin joined the Mayo pathology staff in 1948, as a general surgical pathologist who could diagnose gliomas just as easily as he could carcinoma of the pancreas. Dr. Dahlin made an intensive study of all the bone tumors diagnosed at Mayo Clinic. He kept track of all these tumors by entering the data on 4×6 index cards, which were filed in order of the Mayo Clinic registration number. These studies resulted in Dr. Dahlin’s book on bone tumors, which was published in 1957. The book was an example of clarity and brevity. The skeletal chart, providing the patient’s age and the skeletal distribution of all bone lesions, was Dahlin’s brainchild. Dr. Dahlin received numerous honors, including the first gold medal of the International Skeletal Society. (From Unni KK: David C. Dahlin, M.D. Skeletal Radiol 2004:33:117-118. Reproduced by permission from Springer Science + Business Media.)
Reactive or Post-Traumatic Tumors

PERIOSTEAL ‘DESMOID’ TUMORS

The periosteal desmoid tumor is a fairly common fibrous lesion that most commonly affects boys in the first two decades of life. It arises on the posteromedial aspect of the lower metaphysis of the femur in the region of the attachment of the adductor magnus and the medial head of the gastrocnemius. Imaging studies reveal erosion of the cortex, with a sclerotic base. Microscopically, periosteal desmoids are composed of vascularized and disorganized dense collagenous tissue with uniform unremarkable fibroblasts and admixed reactive immature bone formation (Fig. 18-1).

The lesion almost certainly occurs as the result of previous trauma. It is characteristic in location and does not warrant a biopsy.

NONOSSIFYING FIBROMA (FIBROUS CORTICAL DEFECT; BENIGN FIBROUS HISTIOCYTOMA)

A nonossifying fibroma (NOF) is a very common solitary (but rarely multiple) benign, well-circumscribed, eccentric lesion in the metaphysis of a long bone in a child or adolescent. Most commonly the lower femur and upper or lower tibia are involved (Fig. 18-2). The lesions usually regress spontaneously within 2 or 3 years.

Radiologic surveys have shown a 35% incidence of NOF in normal children. Most clinical cases are detected as incidental findings on imaging studies, although occasionally a patho-

**FIGURE 18-1** A, A scalloped periosteal defect with a sclerotic base in the posteromedial metaphysis of the femur is the characteristic radiographic appearance of a periosteal desmoid tumor, a benign lesion, possibly post-traumatic. B, Photomicrograph of the dense fibrous tissue removed from the lesion illustrated in A. Abundant collagen production by poorly organized but unremarkable fibroblasts has occurred (H&E, × 25 obj.).

**FIGURE 18-2** Location and age distribution of nonossifying fibroma.
logic fracture through a large lesion causes the patient to seek medical attention (Fig. 18-3). The lesions range in size from a few millimeters to several centimeters and are characterized by their cortical, eccentric location, as well as by their well-demarcated central lucency surrounded by scalloped sclerotic margins (Figs. 18-4 and 18-5). Often, an NOF is elongated in the longitudinal axis of the bone. Serial radiographs have demonstrated the migration of the defect away from the epiphyseal plate with time. As the lesions regress, the affected area often shows residual sclerosis (Fig. 18-6).

Gross inspection of surgical curettings reveal fragments of soft, somewhat friable red-brown tissue with foci of yellow discoloration (Fig. 18-7). The microscopic findings include a cellular tissue of unremarkable fibrohistiocytic spindle cells arranged in an interlacing, whorled pattern and interspersed with multinucleated giant cells and islands of pale foamy histiocytes. Hemosiderin deposits and scattered lymphocytes are characteristic features (Fig. 18-8). The microscopic features may on occasion cause diagnostic confusion with other giant cell containing lesions, more especially giant cell reparative granuloma (see Chapter 19). However, the clinical and radiographic presentation of NOF is so typical that it should rarely be confused with anything else.

Although the vast majority of cases of NOF occur in children, very rarely lesions that are histologically indistinguishable from them may be seen in adults, where they are usually reported as benign fibrous histiocytoma or fibroxanthoma. On imaging studies, these adult lesions differ from those seen in children by having less distinct borders and being central rather than eccentric; they may either be lucent or sclerotic, and the bones involved are likely to be different from those seen in children with flat bones more commonly involved in adults (Figs. 18-9 and 18-10). Patients may experience mild pain or they may be asymptomatic. On microscopic examination, however, just as in childhood lesions, the spindle cell stroma has a whorled or ‘storiform’ pattern. The predominant fibrohistiocytic cells are mixed with polygonal histiocytic cells, which have a more vacuolated cytoplasm and may be filled with lipid, hemosiderin deposits, multinucleated giant cells, and sparse chronic inflammatory cells are also evident.
Benign Neoplasms

FIBROUS DYSPLASIA (FIBRO-Osseous Dysplasia; Fibro-Osseous Lesion)

Fibrous dysplasia is a relatively common, slow-growing benign lesion composed mainly of bone and fibrous tissue but occasionally containing foci of cartilage. In 75% of cases, the lesion is monostotic. The femur, tibia, skull and facial bones, or ribs are most commonly affected, but almost any bone can be involved (Fig. 18-11). Involvement of the craniofacial bones may result in marked asymmetry and disfigurement (unilateral cranial hyperostosis) (Fig. 18-12). Rarely, an associated soft tissue myxoma may be present, which is usually intramuscular (Mazabraud's syndrome).
FiGURe 18-8 A, Low-power photomicrograph of a histologic section demonstrates the variegated appearance of a nonossifying fibroma. In some areas, the lesion is more cellular; in others, it has a pink collagenous stroma (H&E, × 1 obj.). B, Low-power photomicrograph of a nonossifying fibroma shows a spindle cell stroma with occasional giant cells and mitoses. Note that the stromal cells are crowded, with little collagen formation (H&E, × 4 obj.). C, Intermediate-power photomicrograph, demonstrating the matted storiform pattern (H&E, ×10 obj.). D, High-power photomicrograph shows foamy cytoplasm in some of the fibrohistiocytic cells and one multinucleated giant cell (H&E, × 25 obj.).
Fibrous dysplasia is most often first seen in children and adolescents, and remains relatively unchanged throughout life, although the lesion may slowly increase in size. Although it has long considered a developmental abnormality, fibrous dysplasia has recently been shown to harbor activating mutations in the alpha subunit of stimulatory G protein (GNAS1), suggesting that the lesion actually represents a benign neoplasm.

In most instances, the condition is asymptomatic, and is discovered incidentally following imaging studies. Rarely a patient with fibrous dysplasia will have symptoms, such as a mass, pathologic...
fracture, or impingement. Deformity may occur because of repeated minor fractures through an affected long bone. (The classic shepherd’s crook deformity of the upper end of the femur is the result of multiple sequential fractures, each of which is followed by some residual deformity [Fig. 18-13].)

On imaging studies, the lesion is usually well defined, although the rim is not usually sclerotic, and the tissue often has a ground-glass appearance owing to the finely scattered bone islands in the lesional tissue (Fig. 18-14). Occasionally cystic changes may be observed within the lesion (Fig. 18-15). Scintigraphy reveals increased isotope uptake in these lesions.

The classic gross appearance of fibrous dysplasia may be seen in Figure 18-16 in a rib, a commonly affected bone in which typically there is fusiform expansion, thinning of the cortex, and replacement...
of bone tissue by a firm, whitish tissue of gritty consistency. Cysts may be large and associated with secondary changes (Fig. 18-17). Microscopic examination reveals irregular foci of woven (non-lamellar) bone trabeculae in a cellular but otherwise unremarkable fibrous stroma (Fig. 18-18). The bony spicules in fibrous dysplasia are often described as resembling the letters C and Y, or Chinese characters. Microscopic evidence of osteoclastic resorption (Fig. 18-19) is frequently associated with these configurations. Osteoblastic rimming of bone, if present, is minimal.

In a few cases, we have observed areas that, instead of immature bone, contained dense blue nodules, or cementicle-like structures, in the fibrous stroma (Fig. 18-20). Occasionally the fibrous stroma exhibits a storiform pattern similar to that seen in a benign fibrous histiocytoma (Fig. 18-21).

Cartilage in lesions of fibrous dysplasia may be either intrinsic to the lesion or secondary to fracture, or may result from disruption of an affected growth plate during childhood. In any event, the amount of cartilage present in the lesion may lead to confusion in diagnosis and the lesion may be mistaken for a chondrosarcoma (Fig. 18-22).

Patients with fibrous dysplasia in addition to islands of cartilage may also exhibit other secondary reactive changes caused by a pathologic fracture. These changes include areas of multinucleated giant cells, foamy histiocytes, and fracture callus (Fig. 18-23). If the reactive areas are the only tissues biopsied, the lesion may be mistaken on histologic examination for a primary neoplasm or even a metastatic carcinoma. Sarcomatous transformation rarely occurs in fibrous dysplasia, but when it does, most often it is following irradiation.

Polyostotic involvement by fibrous dysplasia occurs in about 25% of diagnosed cases. Usually but not always, the multiple lesions affect predominantly one side of the body or a single limb (Fig. 18-24). The histologic features of polyostotic lesions are identical to those of monostotic lesions.

Polyostotic involvement may result in severe deformities, and in a small number of cases, mostly in women, it is associated with patchy skin pigmentation (café au lait, coast of Maine) and various endocrinopathies, usually precocious puberty (Albright-McCune syndrome) resulting from germline mutation in the GNAS1 gene.
FIGURE 18-15  Middle-aged woman who had multiple foci of fibrous dysplasia demonstrating cystic change in the hip (A) and in the tibia (B).

FIGURE 18-16  A, Radiograph of the chest in a 20-year-old man who complained of a swollen area on the seventh right rib. Note the uniform density of the expanded tumor, which is often referred to as a ground-glass appearance. B, The gross photograph of the resected rib reveals a well-circumscribed expansile lesion with a solid white and tan appearance. Note the normal cancellous and cortical bone of the rib on both sides of the lesion. In such a lesion, the cut surface has a gritty consistency due to the presence of fine bone spicules. C, Radiograph of the specimen reveals a relatively lucent expanded zone with marked thinning of the cortex. Throughout the lesion, there is a ground-glass appearance due to diffusely distributed fine spicules of bone.
LIPOSCLEROSING MYXOFIBROUS TUMOR

Liposclerosing myxofibrous tumor (LSMFT) is benign fibro-osseous lesion that has been reported in the intertrochanteric region of the proximal femur.

On imaging studies, the lesion is seen as a centrally located mixed lytic and sclerosing lesion.

The histology shows pagetoid bone with admixed fat, xanthomatous tissue, and fibromyxoid tissue, much of which may be considered reactive. It has been suggested that this lesion represents the end point of a traumatized focus of fibrous dysplasia or other pre-existing benign lesion, which seems to be a reasonable interpretation (Fig. 18-25).

OSTEOFIBROUS DYSPLASIA (DIFFERENTIATED ADAMANTINOMA)

Osteofibrous dysplasia (OFD) occurs almost exclusively in the tibia and/or fibula, although rarely the forearm bones are involved. Although it has been considered in the past to be a variant of fibrous dysplasia, it has a quite different presentation. It is most often seen in young children who present with cortical tumors that may be rapidly enlarging but are usually painless. The deformity of the involved leg may be dramatic, and clinically, the lesion initially behaves in an aggressive fashion. However, the natural history of this lesion is that it behaves less aggressively as the child gets older.

FIGURE 18-17 Photomicrograph of a portion of the lining of a cyst found in a case of fibrous dysplasia shows extensive cholesterol deposition with an associated histiocytic and giant cell response (H&E, x 10 obj.).

FIGURE 18-18 A, Low-power view of curetted fragments from a patient with fibrous dysplasia shows a fibrous tissue stroma with islands of immature bone throughout (H&E, x 1 obj.). B, Photomicrograph of fibrous dysplasia shows a background of collagenized fibrous tissue, within which are irregularly shaped spicules of immature bone. Although bone production is readily evident, there are relatively few osteoblasts rimming the bone spicules. This finding suggests a direct metaplasia of bone from the underlying fibrous tissue (H&E, x 10 obj.). C, The same tissue seen in B viewed with polarized light demonstrates the woven appearance of the collagen within the bone matrix. (This photograph should be compared with the appearance of osteofibrous dysplasia in Figure 18-28.)
**FIGURE 18-19** A, Photomicrograph of tissue obtained from a case of fibrous dysplasia. Note the irregular trabeculae and the osteoclastic activity (H&E, × 4 obj.). B, Photomicrograph demonstrating a feature of fibrous dysplasia not usually illustrated but nevertheless common, that is, osteoclastic resorption of the bone spicules in the fibrous stroma (H&E, × 10 obj.).

**FIGURE 18-20** Photomicrograph showing small, discrete foci of calcified matrix within a case of fibrous dysplasia, which resemble the cementicles occasionally seen in fibromas of the jaw (H&E, × 10 obj.).

**FIGURE 18-21** Photomicrograph of a purely fibrous area within a lesion of fibrous dysplasia demonstrates the whirling pinwheel storiform pattern of benign fibrous histiocytoma (H&E, × 10 obj.).

**FIGURE 18-22** Photomicrograph demonstrating focus of cellular cartilage within fibrous dysplasia. Occasionally, the cartilaginous areas occupy a considerable portion of the lesion and, therefore, can be diagnostically confused with chondrosarcoma; this has been designated by some as fibrocartilaginous mesenchymoma (H&E, × 10 obj.).

**FIGURE 18-23** Photomicrograph taken through an area of fracture in a patient with fibrous dysplasia demonstrates a spindle cell stroma with many giant cells and a sprinkling of chronic inflammatory cells. A biopsy taken through such an area may result in a mistaken diagnosis (H&E, × 10 obj.).
Imaging studies show that the lesion is usually extensive, involving the anterior cortex either of the diaphysis or the metaphysis of the tibia; the epiphysis is usually not affected. Characteristic eccentric intracortical osteolysis, with distortion and thinning of the cortex, is usually evident (Figs. 18-26 and 18-27) and the cortical bone may actually be absent in places. Anterior bowing of the tibia is common, as is a multiloculated appearance. The periosteum is usually well preserved.

The histologic appearance of the affected tissue is somewhat similar to that seen in fibrous dysplasia, with irregular spicules of trabecular bone and unremarkable spindle cells that produce a collagenous stroma. However, in contrast to fibrous dysplasia, the bone spicules are characteristically lined with osteoblasts that may produce a rim of lamellar bone, even though the center of these spicules of bone may have a woven appearance (Fig. 18-28). Foci of hemorrhage and foamy histiocytes, as well as an occasional area of cartilage (usually in the vicinity of a fracture), may be observed.

Using immunohistochemical stains for cytokeratin, it has been shown that in some cases of OFD, it is possible to demonstrate isolated and very occasionally small nests of cytokeratin-positive cells scattered in the matrix. Electron microscopy has demonstrated occasional cells with tonofilaments, even in the absence of cytokeratin-positive stains. In a few cases of OFD, nests of epithelial cells may be readily found without histochemical staining, and these cases have been designated as differentiated adamantinomas (DA) (Fig. 18-29).
These findings indicate that OFD, DA, and adamantinoma, should be regarded as related conditions. However, only rarely does a case of OFD or DA eventually act in a malignant fashion. Genetic studies have also pointed to a relationship between OFD and adamantinoma in that the tumors have been found to share recurrent trisomies (chromosomes 7, 8, 12, and 21). OFD is certainly a distinct entity from fibrous dysplasia. Although most of the cases behave in a benign way, they may need surgery for the correction of deformity. However, it is generally held that surgery should be withheld until after puberty.

**DeSMopLaStiC FiBroMa**

Desmoplastic fibroma is a rare, intraosseous, well-differentiated collagen-producing fibrous tumor characterized clinically by pain. The tumor usually presents during the first three decades of life, and most commonly develops either toward the end of a long bone or in the pelvis or mandible. In most cases, radiographs reveal a lucent defect that may expand the cortex and, on occasion, has a trabeculated appearance due to irregular thinning of the cortex (Fig. 18-30). In some cases, there may be cortical destruction, suggesting a malignant
FIGURE 18-28  A, Photomicrograph of tissue obtained from a patient with osteofibrous dysplasia reveals a cellular spindle cell stroma, with spicules of immature bone. Note the prominent osteoblastic rimming (H&E, × 10 obj.). B, Another field shows focally rimming of more mature bone spicules by osteoblasts (H&E, × 4 obj.). C, In some areas, the surface is covered by more lamellar bone with a core of woven bone. This finding of peripheral maturation is characteristic of osteofibrous dysplasia (polarized light, × 4 obj.). D, In some cases of osteofibrous dysplasia, immunoperoxidase staining shows single keratin-positive cells within the fibrous matrix (Immunoperoxidase CK-AE1/3, × 25 obj.). (A courtesy of Dr. Michael Klein; D courtesy of Dr. Howard Dorfman.)

FIGURE 18-29  In very few cases, there are also rare clusters of keratin-positive cells, occasionally showing keratinization as shown here. In such a case, the term differentiated adamantinoma has been applied (H&E, × 25 obj.).

tumor. Microscopically, the most prominent features are interlacing bundles of dense collagen. The cells are usually sparse and exhibit no cytologic atypia (Fig. 18-31). The histologic similarity of desmoplastic fibroma to certain fibrous lesions elsewhere (such as desmoid tumors) (Fig. 18-32) suggests that it is an intraosseous counterpart of those

FIGURE 18-30  Radiograph of a young adult patient who reported pain in the hip joint reveals a large lytic defect in the ilium, just above the acetabulum. The margins of the lesion are fairly well defined, without obvious sclerosis. On curettage, this lesion proved to be a densely collagenous fibrous tumor, characterized microscopically as a desmoplastic fibroma.
lesions, a contention that is supported by the finding of trisomy 8 and 20 in both tumors. The tumor has a tendency to recur locally but does not metastasize. The lack of bone production in this lesion characteristically distinguishes it from fibro-osseous lesions of bone.

**Malignant Neoplasms**

**FIBROSARCOMA**

Fibrosarcoma is a rare malignant spindle cell neoplasm that produces a sparse to moderate amount of collagen matrix and has no other matrix differentiation. The lesion usually occurs in the metaphyseal ends of the long bones, especially around the knees, in adults who are usually between 20 and 60 years of age (Fig. 18-33). Pain or swelling in the affected area is frequently exacerbated by a pathologic fracture. About one quarter of the reported cases have been associated with a pre-existing condition such as Paget’s disease, fibrous dysplasia, an irradiated giant cell tumor, bone infarct, or long-standing osteomyelitis.

On imaging studies, fibrosarcomas appear lucent often with a mottled or moth-eaten pattern, and frequently there is cortical destruction with extension into soft tissue. The tumor margins are irregular.
Section V  Bone Tumors

and poorly defined (Fig. 18-34). On gross examination, the tumor is usually tan to grayish white, and rubbery in consistency (Fig. 18-35).

On microscopic examination, fibrosarcomas have a characteristic herringbone pattern, and contain homogeneous spindle-shaped fibroblasts with ovoid nuclei. There is relatively little pleomorphism, and mitoses are infrequent (Fig. 18-36). Poorly differentiated tumors with pleomorphic cells, abundant mitotic activity, and bizarre hyperchromatic nuclei are usually classified as malignant fibrous histiocytoma (Fig. 18-37). The well-differentiated tumors grow slowly, and the treatment of choice is radical surgical excision.

The differential diagnosis of primary fibrosarcoma should include leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor; metastatic carcinoma, and metastatic melanoma may also demonstrate a spindle cell pattern (e.g., carcinoma of the kidney); and in this regard, appropriate immunohistochemical studies are essential.

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma was first described in soft tissue about 40 years ago and characterized microscopically by its heterogeneous population of pleomorphic spindle cells organized in a characteristic storiform or ‘starry-night’ pattern.

When these tumors occur in bone, they primarily affect adults, and usually involve the lower femur or upper tibia.

On imaging studies, malignant fibrous histiocytoma appears as a poorly delineated lucent defect, often with cortical destruction.
Minimal periosteal new bone formation may be evident (Fig. 18-38). In some cases this tumor has been found in association with a pre-existing bone infarct (Fig. 18-39).

The characteristic microscopic features of malignant fibrous histiocytoma are bundles and whorls of pleomorphic spindle-shaped cells with patchy or extensive collagen fiber production. The cells and

**FIGURE 18-37** Photomicrograph of a less well-differentiated fibrosarcoma shows cell crowding and pleomorphism typical of a high-grade lesion (H&E, × 10 obj.).

**FIGURE 18-38** Radiograph of the lower femur in a man with a long history of pain, recently increasing in intensity. This extensive lytic and sclerotic lesion proved on biopsy to be a malignant fibrous histiocytoma.

**FIGURE 18-39** A, Lateral radiograph of the femur in a patient with a long-standing history of bone infarction, resulting from his occupation of a caisson worker. More recently, the patient had experienced severe pain in the lower end of the femur, and on the radiograph, a lytic area can be discerned at the lower end of the infarcted zone. B, Photograph of frontally sectioned specimen of the femur removed from the patient in A. The infarcted bone, seen as an area of opaque yellow tissue, is clearly delineated from the surrounding normal bone. The center left portion of the lesion exhibits admixed, fleshy gray tissue that, on microscopic examination, proved to be a malignant tumor.

(Continued)
fibers often meet at right angles, and sometimes take on a pinwheel (storiform) pattern (Fig. 18-40). Foci of rounded cells with a foamy or vacuolated cytoplasm may be observed, together with giant cells and multiple, often atypical, mitotic figures. There is often evidence of phagocytosed intracytoplasmic material, including hemosiderin, hematin, and lipofuscin pigments. An infiltration of chronic inflammatory cells is characteristically present. The heterogeneous microscopic appearance of the tumor suggests a tumor with features of a collagen-producing cell (hence, fibroblast) and a macrophage (hence, histiocyte), but immunohistochemical studies for true histiocytic markers do not support histiocytic differentiation in this tumor, which can best be considered a pleomorphic undifferentiated high-grade sarcoma.

Studies using various immunologic markers have shown that many lesions that had been classified as malignant fibrous histiocytoma are in fact poorly differentiated liposarcomas, or malignant muscle tumors. Therefore before making the diagnosis of malignant fibrous histiocytoma, it is imperative to obtain a suitable panel of immunohistochemical stains.

Although malignant fibrous histiocytoma is not as aggressive as osteosarcoma, it is a fully malignant and metastasizing tumor, and radical treatment is recommended.

Rare instances of multicentricity have been reported.

**ADAMANTINOMA OF LONG BONES**

Adamantinoma is a rare slow-growing neoplasm of long bones, with more than 90% located in the diaphysis of the tibia and most of the rest in the fibula or forearm bones. (It is somewhat similar to the much more common adamantinoma of the jawbones.) Patients with long bone lesions are usually between 20 and 30 years of age. Men are somewhat more frequently affected than women. The principal clinical sign of adamantinoma is the insidious onset of pain and swelling, sometimes developing over many years. The characteristic finding on imaging studies is a multicyclic (soap-bubble) osteolytic lesion with surrounding sclerosis, cortical thinning, and expansion (Figs. 18-41 and 18-42).

On gross inspection, the tumor is generally well circumscribed and rubbery in texture; however, focal areas of hemorrhage or necrosis may be evident. The microscopic finding of a biphasic pattern of spindle-shaped, collagen-producing cells, alternating with sinewy cords or nests of epithelioid cells, sometimes with a squamoid appearance, is characteristic (Figs. 18-43 and 18-44). The epithelioid cells are strongly positive for keratin.

Cytogenetic studies of adamantinoma often show multiple karyotypic abnormalities, but trisomies of chromosomes 7, 8, 12, 19, and 21 are characteristic.

Adamantinoma is a neoplasm of relatively low-grade malignancy. It is locally invasive and may metastasize late in its course in about 20% of cases.

Treatment of adamantinoma consists of adequate surgical excision; the margins of resection should be carefully planned if recurrence is to be avoided, because satellite lesions may occur at some distance from the major tumor mass.

Limited biopsies may result in confusion with metastatic carcinoma or with fibrous dysplasia, however the characteristic clinical presentation should help to avoid this dilemma.
Chapter 18  Fibrous Tumors and Tumor-Like Conditions

Figure 18-42 Anteroposterior (A) and lateral (B) radiographs of a portion of the tibial diaphysis removed from a 9-year-old boy with adamantinoma of the tibia. Small punched-out lesions not connected with the main tumor mass are clearly evident; on histologic examination, each of these lesions contained tumor. When such satellite lesions are found, radical resection is necessary if recurrence is to be avoided.

Figure 18-43 Photomicrograph of an adamantinoma of the tibia shows a fibrous stroma with islands of basophilic epithelioid cells, which may be focally sparse and show cleft-like spaces (as shown in Figure 18-44) (H&E, × 10 obj.).

Figure 18-41 Radiograph of the left leg in a young adult patient who reported aching leg pain shows multiple lytic lesions in the bone, particularly in the lower third of the diaphysis. The lytic, bubbly appearance of the tumor, together with the presence of satellite lesions, is characteristic of adamantinoma in the tibia. Occasionally, adamantinomas may also be seen in the fibula, and even more rarely in the long bones of the forearm.
FIGURE 18-44 A, Photomicrograph of an adamantinoma with a dense fibrous stroma and cleft-like spaces lined with epithelioid cells (H&E, × 4 obj.). B, Higher magnification of an island of epithelioid cells (H&E, × 25 obj.). C, Immunoperoxidase staining shows positivity with CK-AE1/3 (× 10 obj.). (C courtesy of Dr. Howard Dorfman.)
### Benign Nonmatrix-Producing Bone Tumors

**Reactive or Post-Traumatic Tumors, 450**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermoid Inclusion Cyst</td>
<td>450</td>
</tr>
<tr>
<td>Ganglion Cyst of Bone</td>
<td>451</td>
</tr>
<tr>
<td>Unicameral Bone Cyst (Solitary Cyst; Simple Bone Cyst)</td>
<td>453</td>
</tr>
</tbody>
</table>

**Benign Tumors Including Neoplasms, 453**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysmal Bone Cyst</td>
<td>453</td>
</tr>
<tr>
<td>Giant Cell Reparative Granuloma (Solid Aneurysmal Bone Cyst)</td>
<td>456</td>
</tr>
<tr>
<td>Hemangioma of Bone</td>
<td>459</td>
</tr>
</tbody>
</table>

**Skeletal Hemangiomatosis/Lymphangiomatosis**

- (Cystic Angiomatosis of Bone, Lymphangiectasis of Bone), 459

**Eosinophilic Granuloma (Langerhans’ Cell Histiocytosis), 461**

**Lipid Granulomatosis of Bone (Chester-Erdheim Disease), 463**

**Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease), 463**

**Systemic Mastocytosis, 464**

**Giant Cell Tumor, 466**

**Lipoma of Bone, 475**
Reactive or Post-Traumatic Tumors

EPIDERMOID INCLUSION CYST

Epidermoid inclusion cysts are cysts bounded by a wall of stratified squamous epithelium and filled with keratin debris (Fig. 19-1). Although rare, they may occur in bone as the result of a puncture wound or pressure erosion from a subcutaneous lesion when the bone surface is close to the skin. They present on imaging studies as sharply outlined, intraosseous lytic areas with a sclerotic border. They are most commonly found in the distal terminal phalanx (Fig. 19-2) or the calvaria, but examples in larger bones have been reported (Fig. 19-3).

On imaging studies, the differential diagnosis of an epidermoid inclusion cyst in the finger includes enchondroma (which does occasionally occur in the distal phalanx [Fig. 19-4]), giant cell reparative granuloma, acral metastases, intraosseous extension of a glomus tumor (Fig. 19-5), or subungual melanoma.

FIGURE 19-1 A, Photomicrograph of an epidermoid inclusion cyst. The space on the left is lined with stratified squamous epithelium and is filled with keratin debris. In the right half of the photograph, the contents of the cyst have ruptured into the adjacent soft tissue, resulting in a peripheral foreign body histocytic and giant cell reaction (H&E, × 1.25 obj.). B, A higher power view of the cyst wall lined with squamous epithelium (H&E, × 4 obj.).

FIGURE 19-2 Anteroposterior (A) and lateral (B) radiographs showing an epidermoid inclusion cyst. A well-circumscribed lucent defect with a thinned cortical rim is present in the distal portion of the terminal phalanx. No calcification is evident, and this, together with the location, helps to differentiate this lesion from an enchondroma.

FIGURE 19-3 A, Anteroposterior radiograph of the knee in a 71-year-old woman with a several-year history of knee pain. When the knees were imaged, the nonsymptomatic knee revealed the lesion shown here.
Intraosseous ganglion cysts are rare. On imaging studies, they present as well-demarcated uniloculated or multiloculated lytic defects with a thin rim of sclerotic bone. Patients with this disorder are usually middle aged and present with mild, localized pain that is increased by weight bearing. The lesion is most frequently seen at

**GANGLION CYST OF BONE**

Intraosseous ganglion cysts are rare. On imaging studies, they present as well-demarcated uniloculated or multiloculated lytic defects with a thin rim of sclerotic bone. Patients with this disorder are usually middle aged and present with mild, localized pain that is increased by weight bearing. The lesion is most frequently seen at
the epiphyseal end of long bones, commonly in the medial malleolus of the ankle, although the knee and shoulder are other common sites (Figs. 19-6 and 19-7). Despite proximity to a joint, a ganglion cyst rarely involves the joint. (Very rarely an overlying soft tissue ganglion is present on clinical examination, which may communicate with the intraosseous ganglion.)

At surgery, the lesion is lined with a thick, fibrous membrane and filled with a whitish or yellowish gelatinous material. On microscopic examination, the wall of a ganglion cyst is composed of dense, fibrous connective tissue with focal mucoid degeneration, flattened membrane-lining cells, and occasional mononuclear inflammatory cells (Fig. 19-8).

**FIGURE 19-6** A, Ganglionic cyst of bone. In this radiograph of the lower end of the tibia, a well-demarcated, lucent area is evident. Although this lesion is close to the joint space, the joint space is not narrowed; this finding helps to differentiate a ganglionic cyst from an osteoarthritic cyst. B, Anteroposterior radiograph of a knee, showing a well-defined peripheral trabeculated lytic lesion of the lateral femoral condyle, which proved to be an intraosseous ganglion.

**FIGURE 19-7** A, A middle-aged woman with a history of chronic shoulder pain has a lytic lesion in the glenoid, which on an axial magnetic resonance imaging scan (B) shows a bright signal consistent with a fluid-filled cyst. Histology showed this to be a ganglion. The development of a soft tissue ganglion following a labral tear is not uncommon, and the lesion may, as in this case, erode into the bone.
The lack of communication between the cystic defect and the joint cavity, together with the absence of arthritic change, distinguish this disorder from those marginal cysts and subchondral bone cysts commonly associated with degenerative joint disease.

Treatment by curettage or excision has been curative. Recurrences are rare.

**UNICAMERAL BONE CYST (SOLITARY CYST; SIMPLE BONE CYST)**

This is a benign, solitary cystic defect in the metaphyseal region of long bones, usually presenting clinically in children or young adolescents; boys are more commonly affected (Fig. 19-9). The classic location is the proximal humerus, but it is also common in the proximal femur. The usual clinical presentation is a pathologic fracture through the weakened bone.

On imaging studies, the lesion appears as a well-defined central lucent area with a thin sclerotic margin (Figs. 19-10 and 19-11). A pseudoloculated appearance may result from irregular thinning of the cortex by the expanding cyst (Fig. 19-12). Apparent expansion of the bone results from erosion of the cortex by the cyst associated with secondary periosteal new bone formation (Fig. 19-13). However, Codman’s triangle is not a feature of a simple bone cyst, indicating that growth is not rapid. When observed in serial radiographs, the lesion appears to migrate from the epiphyseal plate (although in reality the growth plate grows away from the cyst) (Fig. 19-14).

On both gross and microscopic inspection, an unaltered lesion appears as a clear, fluid-filled cyst lined with a thin fibrous membrane without obvious lining cells (Figs. 19-15 and 19-16). However, because fractures are common complications, secondary changes, such as hemorrhage, hemosiderin deposits, granulation tissue, cholesterol clefts, fibrin, calcification, and reactive bone (Fig. 19-17), may be observed microscopically. In such instances, the lesion may mimic the histologic features of an aneurysmal bone cyst or even a giant cell tumor. A rarely observed focal histologic feature is the accumulation of calcified amorphous material, which superficially resembles the contents of a cementoma of the jaw (Fig. 19-18). This material probably represents calcified fibrin.

Because of the difficulty of complete surgical removal of the lesion, there is a high rate of recurrence after surgical curettage, particularly in children under 10 years of age in whom the lesion is characteristically juxtaepiphyseal. Nonsurgical treatment by aspiration and injection with corticosteroids is now widely used.

**ANEURYSMAL BONE CYST**

An aneurysmal bone cyst is a solitary, expansile lesion that is generally eccentric in location. These lesions are most commonly seen in individuals younger than 20 years of age, and swelling, pain, or tenderness are the usual presenting complaint (Fig. 19-19).
Although involvement of the metaphyseal region of long bones or the spine is most common, any bone can be involved, including flat bones. Approximately 15% of aneurysmal bone cysts arise in the spine, occurring at any level, with the exception of the coccyx. Occasionally multiple vertebrae are affected. Generally the tumor involves principally the vertebral arches; however, occasionally they extend into the vertebral bodies (Fig. 19-20). Extradural cord compression is fairly common and may cause neurologic complications.

When a long bone is affected, serial radiographs generally will demonstrate a rapidly expansile, eccentric, lucent lesion in the shaft of the bone. The periphery of the lesion may often be indistinct, and the tumor itself has a trabeculated appearance. Magnetic resonance imaging studies show the loculated pattern of the lesion and often demonstrate fluid levels.

**FIGURE 19-10** Radiograph of a simple bone cyst in the os calcis. When a solitary bone cyst presents in the calcaneus, it is generally in the anterior portion in contrast to solid tumors such as chondroblastoma, which appear in the posterior portion. (Courtesy of Dr. Robert Freiberger.)

**FIGURE 19-11** A, Radiograph of a simple bone cyst in the proximal humerus. Note that it extends to the growth plate and that there has been a fracture. B, Ten months later, the lesion has greatly expanded. C, Nine months later after curettage and packing with bone chips. (Courtesy of Dr. Robert Freiberger.)

**FIGURE 19-12** Longitudinal section of a segment of resected humerus reveals a well-demarcated cystic cavitation in the medullary portion of the bone, with cortical thinning and periosteal elevation leading to a bulging cortex. Note also the glistening cystic lining. (These lesions usually contain a clear, serous-like fluid.)
On gross examination, the wall of an aneurysmal bone cyst is usually soft and fibrous. When the cyst is opened, separated spaces containing friable, brownish blood clot usually become apparent (Fig. 19-21).

On microscopic examination, the lesion is found to contain cystic spaces of different sizes that are filled with blood but are not lined with vascular endothelium. Between the blood-filled spaces are fibrous septa containing bland spindle cells, giant cells, and foci of immature bone or unmineralized osteoid (Figs. 19-22 and 19-23), together with focal or diffuse collections of hemosiderin, reactive foam cells, and chronic inflammatory cells. Characteristically, the cell morphology appears to be innocuous.

In about half the cases, aneurysmal bone cyst is a secondary reactive lesion, and it is clear from microscopic examination that the lesion coexists with another, usually benign, tumor such as an osteoblastoma, chondroblastoma, nonossifying fibroma, or fibrous dysplasia (Fig. 19-24).

In primary aneurysmal bone cysts, the recent demonstration of translocations involving the \textit{LISP6} gene on chromosome 17 suggest that this lesion is actually a benign neoplasm. The most common translocation is a t(16;17) (q22;p13), which results in fusion of the \textit{LISP6} gene with \textit{CHH11} (a gene encoding osteoblast cadherin), but several other translocation partners have been described. These translocations have not been found in secondary aneurysmal bone cysts. In about 50% of patients, the lesion recurs once or several times after curettage.
It is most important to differentiate this lesion both radiographically and microscopically from a telangiectatic osteosarcoma, a differential diagnosis that may on occasion be very difficult.

GIANT CELL REPARATIVE GRANULOMA (SOLID ANEURYSMAL BONE CYST)

A giant cell reparative granuloma is a benign, intraosseous lesion most commonly seen in the mandible or maxilla but also reported in the small bones of the hands and feet (Fig. 19-25) as well as in other bones. Although these lesions may present in

FIGURE 19-17 A, Photomicrograph of tissue curetted from a simple bone cyst after fracture. Local hemosiderin deposits, chronic inflammation with many cholesterol clefts, and a rapidly forming callus are present (H&E, × 2.5 obj.). B, Higher power view to demonstrate the focal heavy hemosiderin deposition (H&E, × 10 obj.).

FIGURE 19-18 The membranous wall of this simple bone cyst reveals a peculiar, irregularly arranged calcific matrix, which morphologically somewhat resembles the tissue present in a cementoma of the jaw. Such lesions are referred to as cementifying bone cysts, although the material is likely to be calcified fibrin (H&E, × 10 obj.).

FIGURE 19-19 Location and age distribution of aneurysmal bone cyst.

FIGURE 19-19 Location and age distribution of aneurysmal bone cyst.
patients at any age, most are in the second or third decade. The clinical signs are localized pain and swelling of variable duration. Imaging studies reveal a lucent defect expanding the bone. The cortex is frequently thinned and there is little evidence of surrounding sclerosis.

On gross examination, tissue obtained from a giant cell reparative granuloma appears grayish brown and is often friable. Microscopic examination of the tissue reveals varying degrees of cellularity, with predominantly unremarkable fibrohistiocytic spindle cells (Fig. 19-26). Foamy histiocytes and sparse chronic inflammatory cells may also be present. Mitotic activity is rare. Characteristically, giant cells, clustered in areas of recent and old hemorrhage, are scattered throughout the lesion. New bone formation and osteoid may be seen, again usually at sites of hemorrhage.

The differential diagnosis of giant cell reparative granuloma includes the brown tumor of hyperparathyroidism, conventional giant cell tumor, and aneurysmal bone cyst. The following considerations may prove helpful in sorting through the differential diagnosis of a suspected giant cell reparative granuloma. The clinical presentation of a solitary lesion, as well as laboratory findings of normocalcemia and normophosphatemia, mitigate against a brown tumor of hyperparathyroidism. A conventional giant cell tumor has generally a different location from a reparative granuloma, a
more homogeneous morphology, with a diffuse uniform distribution of the giant cells; the stromal cells of a giant cell tumor are more rounded and less spindle shaped, and little or no inflammation is evident. However, the differential diagnosis may be difficult in the case of an involutional giant cell tumor. A giant cell reparative granuloma lacks the large blood-filled channels seen in aneurysmal bone cysts. As with all bone tumors, it is important to note that the typical locations and clinical presentations of the various lesions are different.

**FIGURE 19-23** Photomicrograph demonstrates the many giant cells lining the septa. This feature helps to distinguish an aneurysmal bone cyst lining from the fibrous lining space of a simple bone cyst (H&E, × 4 obj.).

**FIGURE 19-24** A, Radiograph of the forearm, showing an eccentric and expanded cystic lesion of the lower diaphysis of the distal radius. An intact shell of periosteal bone is seen over most of the lesion. In the shaft of the radius, there is a poorly defined central lucency. In this case of aneurysmal bone cyst, there was microscopic evidence of an underlying focus of fibrous dysplasia. B, Gross photograph shows the large blood-filled cavities and extensive hemosiderin staining. C, Photomicrograph demonstrating the juxtaposition of the aneurysmal bone cyst (darker, lower left) and a focus of coexisting fibrous dysplasia (upper right) (H&E, × 10 obj.).

**FIGURE 19-25** Radiograph of a giant cell reparative granuloma of the fourth metacarpal. A lucent lesion expands the bone with thinning and expansion of the cortex. No calcification has occurred. The shaft of the bone protrudes into the expansile lesion, resembling a finger inside a balloon. This radiologic finding is also common in aneurysmal bone cysts when they affect small tubular bones and is evidence of rapid growth.
Although karyotypic abnormalities have been reported in a few cases of giant cell reparative granuloma (suggesting that these, too, represent benign neoplasms), translocations involving 17p of the type seen in primary aneurysmal bone cyst have not been reported to date.

Treatment of a giant cell reparative granuloma consists of curettage or excision of the involved bone; however, recurrences are common in curretted lesions.

HEMANGIOMA OF BONE

Intraosseous hemangiomas are usually asymptomatic. The lesions most often affect the vertebral bodies or the skull, although they may affect any bone, and when they present clinically, it is usually in patients in the middle years of life. There is no familial tendency.

Although hemangiomas are among the most frequently occurring tumors in the vertebral column, they are usually only identified as an incidental finding on imaging studies or after a careful autopsy study; as a clinical cause of disease, they represent only about 2% to 3% of spinal tumors. The most common clinical presentation is that of neurologic symptoms caused by extension of the angiomatic tissue into the epidural space.

Hemangiomas occur most commonly in the lower thoracic vertebrae, somewhat less frequently in the lumbar spine, and infrequently in the cervical spine and the sacrum. Erosion of the horizontal trabeculae of the vertebral bodies leads to a typical radiographic appearance of accentuated, somewhat thickened vertical trabeculae (Fig. 19-27). In children, the affected bone may have a stippled or mottled appearance on radiographic examination. Cortical expansion may be seen in flat bones such as the ribs and skull (Fig. 19-28), and in the skull a characteristic sunburst appearance is often present.

Gross examination of a sectioned hemangioma reveals a cystic, dark red cavity. The microscopic structure of this cavity consists of thin-walled cavernous blood vessels or proliferating capillaries lined with thin, flattened epithelium (Fig. 19-29).

Hemangiomas usually follow an indolent course, but they may be complicated by fracture, extraosseous extension, or hemorrhage. As with vascular tumors in general, hemangiomas of bone may be multifocal within a single bone or in one region of the body.

SKELETAL HEMANGIOMATOSIS/LYMPHANGIOMATOSIS (CYSTIC ANGIOMATOSIS OF BONE, LYMPHANGIECTASIS OF BONE)

Systemic hemangiomatosis/lymphangiomatosis of the skeleton is usually diagnosed incidentally on imaging studies, or as the result of complications such as pathologic fractures, soft tissue masses (rarely), or chylous or hemorrhagic effusions into the pleural cavity.
The patients are usually in the first 3 decades of life at the time of diagnosis. Hemangiomas or lymphangiomas in the skeleton are often seen in association with visceral hemangiomas and lymphangiomas, most commonly involving the spleen, pleura, and skin. There is no known familial tendency.

**FIGURE 19-27** Radiograph of a hemangioma of a vertebral body demonstrates the characteristic, accentuated coarse trabecular pattern of the lesion.

**FIGURE 19-28** Gross photograph of a section through a segment of rib that contains an expanding hemangioma. Both in the rib and in the vault of the skull such lesions may radiographically have a sunburst appearance. (Courtesy of Dr. Miguel Calvo.)

**FIGURE 19-29** A, Lateral radiograph of the right knee of a 15-year-old boy with a 3-month history of pain. B, There is a lytic lesion in the lateral margin of the patella with a sharp margin. C, The curetted tissue shows a capillary hemangioma (H&E, × 4 obj.).
The radiographic features of skeletal hemangiomatosis/lymphangiomatosis are similar to those of solitary hemangiomas. The lytic lesions usually have a fine peripheral rim of increased density (Figs. 19-30 to 19-32).

On gross examination, the lesions are generally cystic, with a reddish fluid indicative of blood or a clear yellow fluid indicating a lymphatic origin (Fig. 19-33). Combinations of hemangiomas and lymphangiomas may be observed. On microscopic examination, the lesions consist of thin-walled vascular spaces lined with flattened endothelial cells and separated by collagen septa.

Laboratory findings in patients with this condition are usually unremarkable, although increases in alkaline phosphatase activity have been reported.

The prognosis for patients with this disorder is variable, depending on the degree and sites of involvement. Rare cases of hemangiomatosis with diffuse blastic skeletal lesions may mimic metastatic cancer; however, in these cases closer scrutiny reveals central lytic areas surrounded by dense sclerotic bone (Fig. 19-34).

EOSINOPHILIC GRANULOMA (LANGERHANS’ CELL HISTIOCYTOSIS)

The clinical presentation and imaging studies in this condition very often suggest malignancy or infection. Despite genetic evidence that Langerhans’ cell histiocytosis is a clonal proliferation of dendritic histiocytes, the clinical course and histopathology favor a reactive process and the essential nature of this disease remains unsettled.
Eosinophilic granuloma of bone may present as a unifocal lesion or as multifocal lesions, sometimes with systemic soft tissue involvement. About 80% of cases of eosinophilic granuloma of bone are solitary. Classically, they present in boys in the first decade of life, and 75% of cases occur before the age of 20 years. The most commonly affected parts of the skeleton are the proximal femoral metaphysis, the skull, mandible, ribs, and vertebral column (Fig. 19-35). Patients may report pain or local tenderness. Laboratory tests are usually unremarkable, although the erythrocyte sedimentation rate may be elevated. Eosinophilic granuloma may also occur in soft tissue, including the skin, oral mucosa, lymph nodes, and lungs. When the lung is affected, patients may develop progressive fibrosis with impaired pulmonary function.

The term Hand-Schüller-Christian syndrome (which originally referred to a classic triad of skull defects, exophthalmos, and diabetes insipidus) is now used to include instances of more chronic evolution, occurring generally in children older than 3 years, with multiple cranial and other bony lesions and sometimes involvement of other systems or with one of the other classic symptoms (exophthalmos or diabetes insipidus). However, the complete triad has been rarely noted in the reported cases.

On imaging studies, one or more circumscribed lytic defects may be evident in a bone (Fig. 19-36). These defects usually lack sclerotic margins. In the spine, collapse of a vertebral body (vertebra plana) is a common presentation (Fig. 19-37). In the long bones, the lesion is usually located in the diaphysis and the cortex is often eroded. Sometimes in long bones, a destructive permeative pattern with periosteal new bone formation can be seen, suggesting malignancy (Fig. 19-38).

Surgical specimens submitted for pathologic examination are usually in the form of multiple curetted fragments, typically consisting of glistening reddish tissue with flecks of opaque yellow material throughout (Fig. 19-39). The tissue is characterized microscopically by a mixture of eosinophils, plasma cells, lymphocytes, and atypical large mononuclear and multinucleated giant cells with abundant pale-staining cytoplasm and indented or cleaved nuclei (Langerhans’ cells). A variable degree of necrosis and fibrosis may be evident,
as may reactive cells such as foamy macrophages. Mitotic activity is minimal (Fig. 19-40). On electron microscopy, the Langerhans’ cell displays characteristic racket-shaped inclusion bodies in the cytoplasm (Birbeck granules) (Fig. 19-41). The Langerhans’ cells are positive for the S-100 protein and CD1A. (Because of the heterogeneity of the lesion, it may occasionally be mistaken microscopically for Hodgkin’s disease.)

Patients with unifocal lesions may show spontaneous regression. If treatment is indicated, then curettage or small doses of radiation for inaccessible lesions is generally used. In general, the prognosis is good if a second lesion does not appear within 1 year. In patients who present with a more systemic illness characterized by fever, organomegaly, and multiple osseous lesions, the course of the disease is likely to be protracted.

Eosinophilic granulomas have been considered as one of a group of disorders known as the histiocytoses, which include also Hand-Schüller-Christian disease and Letterer-Siwe disease; the former is probably better thought of as multiple eosinophilic granulomas, and Letterer-Siwe disease (a rare disease of infants with a characteristically fulminant course) may be an unrelated condition.

**LIPID GRANULOMATOSIS OF BONE (CHESTER-ERDHEIM DISEASE)**

This is a rare disease of adults, mostly in their 40s and 50s, generally characterized radiographically by a diffuse symmetrical sclerosis mainly of the metaphyses and diaphyses of major long bones. Imaging studies have shown coarsening of the trabeculae, endosteal thickening and sometimes cortical rarefaction (Fig. 19-42). Unlike Paget’s disease, no change in the long bony contour is generally seen. The affected individuals may have vague, localizing, aching pain, but this is not always present. In general, these patients do not have hypercholesterolemia.

The first two cases of this condition were described by Chester, a pupil of the Viennese pathologist Erdheim. In one of Chester’s cases, there was also visceral involvement by lipid granulomatosis.

Microscopic examination of the bone shows replacement of the marrow spaces by foamy histiocytes with focal fibrosis, mild chronic inflammation, and new bone formation leading to bony sclerosis, which may have a pagetoid appearance (Fig. 19-43). The microscopic appearance is not diagnostic and, in the absence of imaging studies and clinical correlation, may be interpreted as a healed eosinophilic granuloma or nonossifying fibroma. In some cases, it is possible to find groups of cleaved histiocytes that are S-100 positive, suggesting that Chester-Erdheim disease is related to Langerhans’ cell histiocytosis and is an indolent late stage of the disease.

**SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (ROSAI-DORFMAN DISEASE)**

Sinus histiocytosis with massive lymphadenopathy is generally a systemic disease of teenagers or young adults, distinguished by a proliferation of the distinctive lining histiocytes of the sinusoids
of the lymph nodes, or hematopoietic system, which demonstrate numerous phagocytized lymphocytes within their cytoplasm.

However, when the disease presents in bone, about one third of the cases reported have had no evidence of lymphadenopathy at the time of presentation. Presenting symptoms may be local pain or swelling, which is generally associated with fever and general malaise. On imaging studies, the bone lesions are typically osteolytic and may be confused with either eosinophilic granuloma or malignant lymphoma (Fig. 19-44). With local disease, the prognosis is good; however, it is graver in the presence of widely disseminated disease.

The typical microscopic finding is the presence of large swollen histiocytes with large vesicular nuclei, occasionally prominent nucleoli, and abundant eosinophilic cytoplasm with darker staining in the perinuclear area. Some of the cells demonstrate emperipolesis (active penetration of one cell by another, in contrast to phagocytosis), which is one of the hallmarks of the disease. Most of the internalized lymphocytes are well preserved and located within histiocytic cytoplasm vacuoles. Occasionally, plasma cells, red blood cells, and other hematolymphoid elements also can be present within the cytoplasm of the histiocytes. A foamy appearance of some of the histiocytes is an unusual secondary feature (Fig. 19-45).

The histiocytes in Rosai-Dorfman disease are S-100 protein positive and CD1 negative.

**SYSTEMIC MASTOCYTOSIS**

Systemic mastocytosis is a rare condition that involves the bone and other organs. Although generally a benign indolent disease, exceptionally it may pursue an aggressive course. Bone lesions are...
characterized by both osteoporosis and osteosclerosis, and systemic involvement by hepatosplenomegaly and lymphadenopathy; there may be mast cell infiltration in the skin (urticaria pigmentosa), gastrointestinal tract, heart, and lungs.

Systemic disease may be accompanied by anemia, leukocytosis, leukopenia, eosinophilia, basophilia, or hypocholesterolemia, and because mast cells secrete a variety of biologically active agents, including histamine, heparin, prostaglandins, serotonin, and mucopolysaccharidases, in some individuals, the clinical presentation is characterized by the effects following degranulation of mast cells. Among these effects are flushing, pounding headache, bronchospasm, hypotension, diarrhea, rhinorrhea, urticaria, palpitation, dyspnea, peptic ulcer, and gastrointestinal bleeding.

In patients with skeletal involvement, imaging studies typically show diffuse, poorly demarcated sclerotic and lytic areas involving predominantly the axial skeleton (Fig. 19-46). However, discrete circumscribed lesions can occur, especially in the skull and extremities, and may be mistaken for metastatic disease (Fig. 19-47). In a young person, the condition may first appear as a localized permeative and occasionally sclerotic tumor, and may be mistaken for Ewing’s
sarcoma. In such a case, isotope bone scanning is useful, and both technetium and gallium scans may demonstrate diffuse generalized uptake; gallium in particular is taken up by the mast cells.

Microscopic examination of tissue removed from the bone of patients with mastocytosis shows diffuse or focal replacement of the bone marrow, usually with a mixture of cells including lymphocytes, eosinophils, plasma cells, fibroblasts and increased numbers of mast cells. The latter, however, may be easily overlooked unless a metachromatic stain is performed. Occasionally, the cellular infiltrate is composed predominantly of mast cells. In rare cases in which the mast cells show cytologic features of atypia, it may be confused with lymphoma (Fig. 19-48).

It has been reported that, at least in some cases, mastocytosis results from a point mutation in the proto-oncogene c-kit.

FIGURE 19-40—CONT’D E. Diagram of the various cells seen in eosinophilic granuloma (drawn to scale). Histiocyte (A), plasma cell showing a cartwheel nucleus (B), eosinophil (C), and lymphocyte (D).

FIGURE 19-41 Electron micrograph of a histiocytic giant cell from a patient with eosinophilic granuloma shows a typical Birbeck granule in the cytoplasm (magnification × 100,000).

GIANT CELL TUMOR

A conventional giant cell tumor of bone is a locally aggressive neoplasm most commonly seen in the ends of long bones, usually the lower end of the femur, the upper end of the tibia, or the lower end of the radius. Women are affected about one and a half times more frequently than men. Affected individuals may complain of

FIGURE 19-42 Radiographs of left wrist (A) and lower leg (B) in a 50-year-old female patient with lipogranulomatosis of the bone (Chester-Erdheim disease). Note the patchy sclerosis with coarsening of the trabeculae. Unlike Paget’s disease, the cortex is generally smooth and the bone contour unaffected.
FIGURE 19-43  A, Anteroposterior radiograph of the lower femur and knee joint of a 65-year-old woman with pain in the legs. There is increased density in both femur and tibia. B, Reformatted coronal computed tomography scan highlights the increased bone density. C, Photomicrograph shows replacement of the marrow spaces by fibrohistiocytic tissue. The bone trabeculae are thicker and irregular (H&E, × 4 obj.). D, Higher power shows the irregular cement lines in the bone, giving it a pagetoid appearance. The marrow is filled with bland plump spindle cells, many having a vacuolated cytoplasm (H&E, × 10 obj.). E, Higher power view of D (H&E, × 25 obj.). F, The plump vacuolated spindle cells are positive for CD68 (Immunoperoxidase, × 25 obj.).
pain, show signs of local swelling, or have a pathologic fracture through the lesion. Multicentric lesions have been reported but are extremely rare (Fig. 19-49). In those rare cases in which the jaw or the spine is involved, evidence of pre-existing Paget’s disease should be sought. Primary cases of giant cell tumor in the axial skeleton are characteristically seen in the sacrum of young women. Giant cell tumor most often occurs in the third and fourth decades of life, and is rare in skeletally immature subjects. Rare cases have been

**FIGURE 19-44** A, Lateral radiograph of the arm of a 26-year-old man with localized diaphyseal lucency, which on biopsy, proved to be Rosai-Dorfman disease. The differential diagnosis included eosinophilic granuloma, malignant lymphoma, infection, and metastasis. B, A 32-year-old man with recent back pain on radiographic examination was shown to have a well-defined lytic lesion of the left ilium with a sclerotic margin, suggesting a benign process such as fibrous dysplasia, chondromyxoid fibroma, or fibroxanthoma. Biopsy revealed Rosai-Dorfman disease. (A courtesy of Dr. Howard Dorfman.)

**FIGURE 19-45** A, Photomicrograph reveals a mixed cell population of a few distinctive histiocytes with abundant eosinophilic cytoplasm and round to oval nuclei with prominent nucleoli. Admixed with these cells are plasma cells and lymphocytes (H&E, × 10 obj.). B, Some of the histiocytes show well-preserved lymphocytes or neutrophils within their cytoplasm (emperipolesis) (H&E, × 25 obj.).
**Figure 19-45—Cont’d**

C. The typical appearance of the histiocytes in Rosai-Dorfman extranodal sinus histiocytosis is of cells with large vesicular nuclei, occasional prominent nucleoli, and abundant eosinophilic cytoplasm with darker staining in the perinuclear area (H&E, × 25 obj.).

D. Immunoperoxidase staining using CD68 antibody reveals positive histiocytes throughout the lesional tissue (× 10 obj.).

E. Immunoperoxidase staining using CD64 antibody confirms the presence of histiocytes (× 10 obj.).

F. Immunoperoxidase staining using S100 protein antibody labels the lesional histiocytes (× 10 obj.).

(A, B, and C courtesy of Dr. Mark Edgar.)

**Figure 19-46**

A. Computed tomography scan of sacrum and pelvis of a 70-year-old man complaining of pain in the buttock of recent origin. There is patchy bony sclerosis with focal osteolysis. The presumptive diagnosis was metastatic carcinoma.

B. A biopsy of the ileum revealed a mixed fibrous and inflammatory infiltrate of the marrow space, but no evidence of tumor; many of the mononuclear cells had a granular cytoplasm, which stain with Giemsa in this case of mastocytosis (Giemsa, × 25 obj.).
FIGURE 19-47  

**A**, Radiograph of a 14-year-old girl with a 6-month history of pain in the hip, which proved histologically to be caused by a mastocytoma. 

**B**, Photomicrograph of tissue obtained from the case demonstrated in the radiograph in **A**. The rounded bizarre cells with abundant cytoplasm and many giant cell forms suggested a malignancy, although careful searching showed no mitotic figures. Electron microscopic studies in this case confirmed the presence in the cells of typical mast cell granules (H&E, × 25 obj.). (Courtesy of Dr. Edward McCarthy, Baltimore, MD.)

FIGURE 19-48  

**A**, A 42-year-old man with osteoarthritis underwent right total hip replacement. Clinically he was anemic. 

**B**, Photomicrograph demonstrates sheets of pale vacuolated cells focally replacing the bone marrow. Note that there is some thickening of the trabeculae, which reflects the spotty diffuse sclerosis often seen in clinical radiograph of patients with mast cell disease (H&E, × 4 obj.). 

**C**, A higher power photomicrograph shows the large foamy cells with bland nuclei and a faintly granular cytoplasm (H&E, × 10 obj.). 

**D**, Strongly positive staining with immunoperoxidase using anti-mast cell tryptase (× 25 obj.). (These cells were also reported as being strongly positive when CD117 was used.)
reported in children, in whom the growth plate is active and the lesions were metaphyseal in location.

Imaging studies generally reveal a well-defined defect in the metaphysis and epiphysis that is usually eccentrically located and extends to the subchondral bone end plate of the articular surface. There is usually no evidence of sclerosis around the lesion (Figs. 19-50 and 19-51). Occasionally the lesion may have an aggressive radiographic appearance, but generally, this does not correlate with aggressive histologic features or prognosis.

Grossly, the unaltered lesional tissue appears rather homogeneous, with a tan color and a moderately firm consistency (Fig. 19-52). However, foci of hemorrhage or necrosis may be observed in many tumors.

The microscopic examination of the tumor shows a background of proliferating, homogeneous mononuclear plump stromal cells, which have a round to ovoid nuclei, with evenly distributed chromatin and prominent nucleoli; dispersed evenly throughout the tissue are multinucleated giant cells, some having vacuolated cytoplasm (Fig. 19-53). Focal areas with spindle cell and even a storiform pattern may be present giving the appearance of benign fibrous histiocytoma (Fig. 19-54). Vascular invasion by the tumor is commonly seen. In many cases, foci of reactive bone are present, particularly at the periphery of the tumor (Fig. 19-55), and in yet other areas, involutonal changes with lipid-filled histiocytes may be observed (Fig. 19-56). These infrequent patterns may give rise to occasional problems in differential diagnosis.

Immunohistochemical studies indicate that the giant cells in giant cell tumors that express histiocytic markers are reactive cells recruited to the tumor by the neoplastic mononuclear cells that release RANK ligand, a trophic factor for osteoclasts.

After curettage, conventional giant cell tumors have a high local recurrence rate (50%). Therefore, surgical excision is the treatment of choice. In conventional giant cell tumors, lung metastases only rarely appear and usually can be successfully treated by surgical excision (Fig. 19-57).

Malignant dedifferentiation within a conventional giant cell tumor has long been recognized as an occasional complication of radiation therapy. The interval between radiation and the diagnosis of malignancies has varied between 1 and 25 years, with an average interval of 8 years. Dedifferentiation within a conventional giant cell tumor occurring in the absence of prior radiation therapy is extremely rare.

Microscopically, malignant transformation is characterized by the presence of focal areas of anaplastic pleomorphic tumor cells and atypical mitoses; it is necessary that there are areas of identifiable conventional giant cell tumor present or, in the case of postradiation sarcoma, that the prior diagnosis of giant cell tumor be confirmed (Fig. 19-58). It is important to note that vascular invasion, soft tissue extension, and high mitotic activity do not in themselves establish malignancy.
Malignant degeneration in giant cell tumor should be regarded in the same way as malignant degeneration/dedifferentiation described in other soft tissue and osseous neoplasms, such as low-grade osteogenic sarcoma, enchondroma and low-grade chondrosarcoma, and even in pigmented villonodular synovitis.

Conventional giant cell tumor of bone frequently demonstrates telomeric associations by conventional cytogenetics (i.e., a tendency for the telomeric ends of chromosomes to associate with one another), but so far, a specific genetic signature has not emerged.
FIGURE 19-53  

A, Photomicrograph of a conventional giant cell tumor reveals the cellular nature of the lesion and the giant cells that are evenly distributed throughout. (The presence of giant cells alone does not confirm the diagnosis of a giant cell tumor. Many lesions contain giant cells; it is the combination of mononuclear stromal cells and giant cells that is diagnostic of giant cell tumor.) (H&E, × 4 obj.)  

B, Another field of the same tumor demonstrates the homogenous, mononuclear stromal cells and the evenly distributed multinucleated giant cells (H&E, × 10 obj.).  

(C) High-power picture of another field compared with the previous photomicrograph; some of the giant cells are much larger and appear to be phagocytosing adjacent mononuclear cells (H&E, × 25 obj.).

FIGURE 19-54 It is not unusual in giant cell tumor to see a focal spindling out of the stromal cells, which form a storiform pattern similar to that seen in a nonossifying fibroma or benign histiocytoma (H&E, × 10 obj.).

FIGURE 19-55 Photomicrograph demonstrating irregular and extensive bone formation in the periphery of an otherwise typical conventional giant cell tumor. Such an appearance should not be confused with a giant cell–rich osteosarcoma (H&E, × 10 obj.).
FIGURE 19-56 Photomicrograph of tissue obtained from a giant cell tumor of long standing shows foci of lipid-laden macrophages, fibrosis, and chronic inflammation. In some cases, especially following fractures, such involutional areas may be widespread (H&E, × 10 obj.).

FIGURE 19-57 Photomicrograph to show a nodule of metastatic conventional giant cell tumor in the lung. Note that at the edge of the tumor nodule there is bone formation (H&E, × 4 obj.).

FIGURE 19-58 A, Photomicrograph showing conventional giant cell tumor on the lower left and dedifferentiated tumor on the upper right (H&E, × 10 obj.). B, Within the dedifferentiated tumor, there is an atypical mitosis and cells with large nuclei and clumped chromatin (H&E, × 25 obj.). C, In other areas of the dedifferentiated tumor, malignant bone matrix formation is present (H&E, × 10 obj.).
LIPOMA OF BONE

Benign fatty tumors of bone are among the rarest skeletal tumors. They have been described in patients of all ages, especially in the long bones. They may present as either subperiosteal or intramedullary lesions. In either case on imaging studies, they are lytic, although occasionally calcification within necrotic fat may give rise to confusion with a bone infarct (Fig. 19-59).

The intramedullary lesions have well-defined borders and occasionally a bubbly appearance. The periosteal lesions are also lytic and usually erode the cortex. On gross examination, the tumor is characteristically a lobulated, soft, yellow mass. Microscopic examination reveals mature fat, usually containing thin, residual cancellous bone trabeculae (Fig. 19-60). A 3;12 translocation common in soft tissue lipomas has been demonstrated in a parosteal lipoma.

FIGURE 19-59 A, Radiograph of an ankle shows fusiform swelling of the lower end of the fibula due to a lytic trabeculated intraosseous mass. In the center of the lesion, there is focal dense calcification. B, Photograph of a section through the dissected distal fibula shown in A. The lesion is composed of an admixture of fat and fine cancellous bone. C, Photomicrograph of tissue from the densely calcified area seen on the radiograph A shows heavily calcified scarring of necrotic fat within the lipoma (H&E, x 4 obj). D, Photomicrograph of the lesional tissue in another area of the specimen shown in B, demonstrating punctate calcification within an area of fat necrosis (H&E, x 25 obj). (Courtesy of Dr. Leonard Kahn.)
FIGURE 19-60 (A) Radiograph of a 60-year-old man who reported pain in the heel shows a well-defined lytic lesion with a sharp border. (The pain may well have resulted from the heel spur.) B, Photomicrograph of the curettings show a fatty tumor with included flecks of bone (H&E, × 10 obj.). (Courtesy of Dr. German Steiner.)
CHAPTER 20

Malignant Bone Tumors

Thomas Hodgkin (1798–1866). Hodgkin was one of the most prominent physicians of his time and a pioneer in preventive medicine. He is now best known for the first account of Hodgkin's disease, a form of lymphoma, in 1832. Hodgkin's work marked the beginning of times when a pathologist was actively involved in the clinical process. Hodgkin was born to a Quaker family, and in September 1819, was admitted to St. Thomas' and Guy's Medical School. He also studied at the University of Edinburgh, Scotland, where in 1823, Hodgkin qualified for his medical degree. Hodgkin was a close friend of Sir Moses Montefiore, and he accompanied him to Palestine in 1866. There he contracted dysentery and died on April 4, 1866; he is buried in Jaffa. (From Thomas Hodgkin. Wikipedia. Available at http://en.wikipedia.org/wiki/Thomas_Hodgkin.)

James Stephen Ewing (1866, Pittsburgh–1943, New York City). At age 14, Ewing suffered from osteomyelitis of the femur, which confined him to bed for 2 years. While bed bound, he entered a competition and won a microscope, the instrument that was to play a strong role in his future interests in cancer. Ewing attended Amherst College. In 1888, he was accepted into the College of Physicians and Surgeons of New York, and graduated from the College 3 years later. In 1899, Ewing was appointed the first Professor of Pathology at Cornell University, a position that he kept for 33 years. Ewing was a cofounder of the American Association for Cancer Research in 1907, and in 1913, cofounded the American Society for the Control of Cancer (now the American Cancer Society). Ewing's textbook Neoplastic Diseases was published in 1919. The following year at a meeting of the New York Pathological Society, Ewing presented his paper on the malignant bone tumor that later became known as Ewing's sarcoma. He responsible for the creation of Memorial Sloan-Kettering Cancer Center in New York City. James Ewing died from bladder cancer at the age of 76. (From the Wellcome Library, London.)

| Solitary (Localized) Myeloma (Plasmacytoma), 485 |
| Vascular Neoplasms, 485 |
| Well-Differentiated Endothelial Neoplasms, 487 |
| Poorly Differentiated Endothelial Neoplasms, 489 |
| Hemangiopericytoma, 490 |
| Metastatic Cancer, 492 |

Ewing's Sarcoma (Primitive Neuroectodermal Tumor), 478

Immunohematopoietic Neoplasms, 481

Primary Non-Hodgkin's Lymphoma, 481

Hodgkin's Disease, 483

Leukemia, 483

Multiple Myeloma, 484
Ewing’s Sarcoma (Primitive Neuroectodermal Tumor)

Ewing's sarcoma is a small cell malignant neoplasm of bone that develops in the diaphysis or metaphysis of long bones, especially the femur, tibia, and humerus, as well as in the pelvis and ribs. It is essentially a tumor of childhood, with most patients being younger than 20 years of age; boys are more commonly affected than girls (Fig. 20-1). Rarely Ewing's tumors may arise in soft tissues. In the past, the term primitive neuroectodermal tumor has been often applied to extraskeletal Ewing's sarcoma, but based on shared molecular features (vide infra), these two tumors are now considered a single pathologic entity.

Patients usually report pain or tenderness in the affected bone of several weeks' or months' duration. Physical examination may reveal swelling and tenderness. Fever, anemia, leukocytosis, and elevated erythrocyte sedimentation rates often initially suggest a diagnosis of osteomyelitis, and because of the radiologic and microscopic appearance of the tumor, osteomyelitis may on occasion be the most important microscopic differential diagnosis.

Imaging studies usually reveal a lytic, moth-eaten, mottled appearance, or sometimes even sclerosis (Figs. 20-2 and 20-3); classically a laminated periosteal reactive bone is present on the surface (onion skin) (Fig. 20-4). Both magnetic resonance imaging (MRI) and computerized tomography (CT) provide better pretreatment assessment of the intramedullary and soft tissue infiltration of the tumor, which are often much greater than is suggested on plain films.

Gross examination of intact specimens reveals poorly demarcated, grayish white tumor tissue with areas of hemorrhage, cystic degeneration, and necrosis. The extent of the tumor is usually greater than that evident on radiographs, and extension of the tumor into adjacent soft tissue is common.

On microscopic examination, Ewing's sarcoma consists of a homogeneous population of densely packed small cells. Nuclei are regular with a round to oval shape and finely granular nuclear chromatin and one or two small nucleoli. The cell membrane is indistinct in histologic sections but may be visible on tissue-touch imprints. The cytoplasm is generally delicate and lace-like. Mitoses are relatively infrequent (Fig. 20-5). Reticulin fibers (type 3 collagen) are sparse, but glycogen is evident after periodic acid–Schiff staining in more than 70% of cases and is usually found to be abundant on ultrastructural examination (Fig. 20-6). Areas of hemorrhage and necrosis are typically present. Scattered dark apoptotic cells as well as nests of small pyknotic cells are typically found as are foci of tissue necrosis. Although commonly referred to as a small cell tumor, Ewing's cells are actually two to three times larger than lymphocytes. Most Ewing's tumors will show positivity for the CD99 antibody in a diffuse membranous pattern. As well as vimentin, they may also demonstrate neuron-specific enolase, S-100 protein, and other neural markers. Electron microscopy may demonstrate neurosecretory granules.

FIGURE 20-1 Location and age distribution of Ewing’s sarcoma.

FIGURE 20-2 Radiograph of a 9-year-old child who reported pain in the hip joint shows a permeative destructive lesion of the ischium. Biopsy of this area showed a malignant round cell tumor consistent with Ewing's sarcoma.
Reciprocal translocation between chromosomes 11 and 22 involving bands q24 and q12 t(11;22)(q24;q12) occurs in the majority of cases and is also present in the related small cell peripheral neuroectodermal tumors and Askin's tumors. These cytogenetic techniques are effective when fresh tumor tissue is available, but demonstration of this translocation can also be achieved by reverse transcriptase polymerase chain reaction employing fixed tissue when fresh tissue is not available. Furthermore, fluorescence in situ hybridization techniques are now routinely used to demonstrate rearrangement of the Ewing's sarcoma locus (EWSR1) by employing a break-apart probe that generates two spatially separate fluorescent signals when the gene has been rearranged as the result of translocation.
Section V  Bone Tumors

The microscopic differential diagnosis of Ewing's sarcoma includes osteomyelitis, eosinophilic granuloma, and the group of small cell tumors that includes lymphoma, leukemia, metastatic neuroblastoma, and embryonal rhabdomyosarcoma. However, with molecular probes and immunohistochemical techniques, differentiation between these entities generally no longer presents significant problems (Fig. 20-7).

Ewing's sarcoma has a high incidence of early metastatic spread, usually to the lungs or to other bones. However, the use of adjuvant
chemotherapy with radiation and surgical resection has considerably improved the outlook for patients with this tumor.

**Immunohematopoietic Neoplasms**

In cases of primary lymphoma, secondary involvement of the bone is present in approximately 20% of all patients; in all types of leukemia, a diffuse involvement of the bone marrow is a feature. Primary intraosseous lymphomas are rare, but patients presenting with primary bone lymphomas and no systemic involvement have a substantially better prognosis than those with disseminated disease (Fig. 20-8).

Primary bone lymphoma may occur at any age but is unusual in patients during the first decade of life. Although local pain is the usual presenting symptom, the overall general health of the patient is good. Early changes on imaging studies include vague, mottled lucent areas; however, in long-standing lesions, there may be considerable bone destruction. Microscopic identification depends on the presence of cells of the lymphoid series that solidly pack the marrow space; a specific diagnosis depends on the identification of the immunologic phenotype of the cell involved.

**PRIMARY NON-HODGKIN’S LYMPHOMA**

Primary non-Hodgkin’s lymphomas of bone are usually large cell lymphomas of B-cell origin. They usually present in the axial skeleton or in the bones of the extremities. They occur mostly in patients older than 20 years of age (more than 50% of these tumors occur in patients older than 40 years of age). There is a slight male predominance. Some cases present with multifocal lesions. The characteristic clinical picture is that of a patient in generally good health but who reports localized pain, swelling, or tenderness. No fever or marked weight loss is noted in the typical case. An appropriate staging procedure is required to rule out extraskeletal disease.

On imaging studies, osteolysis is the predominant change observed, with the resulting appearance of a moth-eaten destructive lesion with no periosteal reaction (Fig. 20-9). Radionuclide bone scan as well as MRI and CT help evaluate the extent of the lesions; especially soft tissue extension. Gross examination reveals grayish white (fish flesh) tissue infiltrating the bone (Fig. 20-10).

Microscopically, the tumor consists of sheets of lymphoid cells with variable nuclear characteristics that depend on the type of lymphoma (Fig. 20-11). However, most commonly, primary lesions are of the diffuse large cell type and have a polymorphonuclear appearance, with large cells having irregular cleaved nuclei, large cells with oval nuclei containing prominent nucleoli, and medium to small cells with cleaved, hyperchromatic nuclei. In addition to Ewing’s tumor, the differential diagnosis includes poorly differentiated metastatic carcinoma, melanoma, and if the tissue is poorly preserved, osteomyelitis.
A panel of immunologic markers is necessary for positive identification of cell type, including leukocyte common antigen, CD20 (a pan B-cell marker), CD45Ro as a T-cell marker, and Ki1 (CD30) for the rare large cell anaplastic lymphoma. It is worth noting that lymphoblastic lymphoma (which may present in childhood as an osseous lesion) is frequently positive for CD99 but negative for most B-cell markers, which can result in confusion with Ewing's sarcoma. This tumor is best identified by nuclear staining for terminal deoxynucleotidyl transferase.

**FIGURE 20-9** A 45-year-old man reported sudden onset of pain in the left arm. Radiograph shows a pathologic fracture through an area of permeative destruction of both the cortical and medullary bone, which proved on biopsy to be due to lymphoma. The fracture is recent, and there is little or no periosteal reaction either to the tumor or to the complicating fracture. Biopsy showed a large B-cell lymphoma.

**FIGURE 20-10** An amputated toe from a patient with a primary non-Hodgkin's lymphoma of the bone. The middle phalanx has been completely destroyed by a fleshy pink tumor, which has extended both dorsally and ventrally into the soft tissue.

**FIGURE 20-11** A, Low-power photomicrograph of an area of non-Hodgkin's lymphoma shows the crowded, irregular mixed cell population (H&E, ×4 obj.). B, At high power, there are both larger cells, frequently showing nuclear indentation and clefts, and admixed lymphocytes. Compared with the cells of Ewing's tumor, the cells are larger and the cytoplasmic borders are more distinct. The cells in a non-Hodgkin's lymphoma usually lack glycogen (H&E, × 25 obj.). C, Reticulin staining of the tumor shown in A reveals a fine network of reticulum separating small groups of cells as well as individual cells (× 10 obj.). Appropriate antibodies further help to subclassify the cell types.
The use of nonlymphoma markers such as keratin, desmin, and smooth muscle actin can help rule out other small cell tumors. The majority of cases of non-Hodgkin's lymphoma have clonal chromosomal abnormalities with complex numerical and structural changes.

**HODGKIN'S DISEASE**

Hodgkin's disease may involve bone secondarily and present with bone pain, tenderness, and sometimes with a palpable mass. However, primary osseous involvement is rare. The vertebral and pelvic bones are most commonly affected, but lesions may appear anywhere in the skeleton. Vertebral involvement may result in neurologic symptoms.

The radiographic features of Hodgkin's disease in the bone are variable; lesions may be lytic, blastic, or mixed. The radiologic finding of a dense ivory vertebra is a classic presentation (Fig. 20-12). Usually multiple bones are involved, even if this is not apparent radiographically.

Microscopically, a characteristic mixed cell population can be observed, including plasma cells, lymphocytes, histiocytes, and eosinophils (Fig. 20-13). Large, irregular mononuclear cells are also present, and should alert the observer to the possibility of Hodgkin's disease. A large amount of fibrous stroma may complicate the diagnostic process. The pathognomonic and necessary finding in Hodgkin's lymphoma is the Sternberg-Reed cell. The Sternberg-Reed cell is large, with sharply delineated, abundant cytoplasm and a mirror image double nucleus having large, prominent, central eosinophilic nucleolus (Fig. 20-14). Conventional Sternberg-Reed cells express CD15 and CD30. The differential diagnosis in Hodgkin's disease may be difficult and especially with reactive or inflammatory conditions. The positive identification of Sternberg-Reed cells is therefore essential.

**LEUKEMIA**

Diffuse involvement of the bone marrow is a hallmark of all types of leukemia. Skeletal pain constitutes the presenting complaint of a significant number of children but fewer adults. Radiographic bone changes ultimately occur in 70% to 90% of leukemic patients and are described as (1) a transverse lucent metaphyseal line in children, (2) osteolytic destruction, (3) periosteal elevation, (4) generalized osteopenia, or (5) focal sclerosis.

A characteristic finding in children is a radiolucent band in the metaphysis of the long bones; similar bands may be found in the vertebral bodies just beneath the end plates (Fig. 20-15). Perhaps the most common radiographic finding in both children and adults is diffuse demineralization of the spine with compression fractures, usually seen as anterior wedging. Epidural extension of the tumor with neurologic complications is not uncommon in leukemia, and sometimes constitutes the presenting symptom. Replacement of bone marrow by leukemic tissue may lead to ischemic necrosis of the affected bone and bone marrow (Fig. 20-16). Radiographic periosteal elevation is caused by subperiosteal leukemic masses. Sclerotic lesions are rare
Bone Tumors

and are usually juxtaposed with lytic lesions. Radiographic features may mimic Ewing’s sarcoma and other round-cell lesions.

The clinical diagnosis is especially difficult when a solid tumor develops significantly before the characteristic hematologic changes of leukemia. Solid leukemic tumors are found in as many as 40% of cases at autopsy, and they are the presenting feature of leukemia in up to 2% of cases.

Myelogenous leukemia can produce solid tumors called chloromas or granulocytic sarcomas. Granulocytic sarcomas are collections of myelogenous leukemic cells outside of the bone marrow. (Their characteristic yellow-green color is frequently absent, so granulocytic sarcoma is a more accurate name for these leukemic tumors than is chloroma.) Granulocytic sarcomas are most commonly found in the orbit and long bones, as well as in perineural spaces, lymph nodes, ovaries, and kidneys.

Wright-Giemsa and chloracetate esterase stains sarcomas well as CD33, 34, 43, 45, 68, and Ki67 have all been helpful in diagnosis of these difficult tumors. The Philadelphia chromosome translocation t(9;22)(q34;q11) is associated with chronic myeloid leukemia. Immunostain for myeloperoxidase may also be positive.

Myelofibrosis, which is often a precursor of leukemia, is discussed in Chapter 9.

**MULTIPLE MYELOMA**

Multiple myeloma is by far the most common primary tumor of bone, with a predilection for marrow-containing bones. The spine is almost always involved, although the primary presentation may be in the skull, ribs, sternum, or pelvis. Multiple myeloma usually affects individuals older than 50 years of age but is occasionally seen in patients at a younger age; men are affected almost twice as often as women. The usual clinical picture is one in which pain predominates. Anemia is common, the erythrocyte sedimentation rate is usually elevated, and occasionally, especially in association with bed rest and concomitant osteoporosis, hypercalcemia may be present. The most important diagnostic test involves the identification of a monoclonal protein (immunoglobulin G or immunoglobulin A) by serum electrophoresis (Fig. 20-17). Light-chain subunits of immunoglobulins (Bence Jones proteins) are usually found in the urine resulting in renal insufficiency. In more than half of patients, pathologic fractures

**FIGURE 20-15** A, Anteroposterior radiograph of the knee in an infant with recent onset of fever, showing a radiolucent zone in the metaphysis adjacent to the growth plate, which is a classic radiologic sign of acute leukemia. B, Photomicrograph to demonstrate replacement of the majority of the bone marrow by lymphocytic leukemia (H&E, × 4 obj). C, Somewhat higher power shows normal bone marrow (upper right) and the uniform monotonous lymphocytic infiltrate (lower left) (H&E, × 10 obj).
lead to an overall loss of vertebral body height, with swelling of the adjacent intervertebral discs into the affected bodies and a resulting fish-mouth appearance (Fig. 20-18).

On imaging studies, multiple myeloma is characterized by the presence of round lytic defects in the bone, with no significant sclerotic reaction surrounding them (Fig. 20-19). Occasionally, however, lytic defects may not be apparent and the radiographic picture suggests a diffuse osteopenia. In such cases, the differential diagnosis from osteoporosis must be made by laboratory examination.

Gross examination of the affected bones reveals either a diffuse gelatinous red infiltration of the marrow or discrete tumor nodules (Fig. 20-20). Microscopic examination reveals sheets of plasma cells, which may exhibit various degrees of differentiation; however, the atypicality of the cells (Fig. 20-21) has no prognostic significance. In multiple myeloma, the deposited proteins are related to the light change immunoglobulin (κ or λ). In approximately 10% to 15% of patients with myeloma, amyloidosis occurs as a complication and amyloid deposits can be found within the bone (Fig. 20-22). CD138 and plasma cell–associated antigen are typically positive. Numerous genetic aberrations have been described, but the most common is t(11;14)(q13.3 q32.3).

Multiple myeloma is a strikingly aggressive tumor, which in the past led to early death. However, palliative chemotherapy and bone marrow transplantation have been effective in prolonging the survival time.

Very rarely, multiple myeloma produces sclerotic radiologic lesions, such that the correct diagnosis may not at first be considered. (Sclerotic lesions are typical of the rare POEMS syndrome in which Polyneuropathy, Organomegaly, Endocrinopathy, an M-component spike on electrophoresis of the serum, and Skin changes are characteristic.) Patients with this condition are generally younger than those with multiple myeloma and often present with peripheral neuropathy. Generally, the disease affects the axial skeleton and the appendicular skeleton and the skull are spared. The true diagnosis in such cases may be delayed for a long time.

**SOLITARY (LOCALIZED) MYELOMA (PLASMACYTOMA)**

The occurrence of a large solitary focus of plasma cell proliferation associated with radiologic evidence of bone destruction can be considered as a distinct entity if the following criteria are met: (1) there are no other radiographically evident lesions; (2) a bone marrow biopsy from a site other than the solitary focus reveals no malignant cells; and (3) no significant protein or immunoglobulin abnormality is discernible in the serum or on urine analyses (or, if a monoclonal spike is present on serum electrophoresis, this disappears after treatment of the solitary lesion).

Patients who meet these criteria tend to be younger than those with multiple myeloma and have a better prognosis. As with multiple myeloma, men are more often affected. The site of involvement is usually a long bone or a vertebral body (or, in exceptional cases, the lesion is confined to soft tissue). Long bone lesions may be expansile and often present with a pathologic fracture (Figs. 20-23 and 20-24).

In the spine, solitary myelomas are likely to present with rapidly developing paraplegia and gibbus deformity as a result of vertebral collapse (Fig. 20-25). (In fact, paraplegia is much more frequently associated with solitary myeloma than with multiple myeloma, probably because patients with multiple myeloma tend to die before paraplegia can develop.) However, paraplegia is by no means always present and the patient may present with only pain, as was the case illustrated in Figure 20-26.

More than half the patients who present with an apparently solitary focus of myeloma develop multiple myelomatosis and eventually die of disease. A few cases may develop generalized disease only after many years. The remaining patients may be cured after radiation therapy or surgical en bloc resection. Microscopically, the tissue obtained in a case of solitary myeloma may range from well differentiated to poorly differentiated plasma cells; however, it does not seem that this variation affects the prognosis in these patients.

**Vascular Neoplasms**

Vascular neoplasms of bone are rare. The current classification scheme is controversial but includes three basic categories: benign (hemangioma; see Chapter 19), fully malignant (angiosarcoma), and tumors of intermediate malignancy (hemangiendothelioma). The presence of multiple intraosseous lesions at the time of initial diagnosis is common in both well-differentiated and poorly differentiated tumors. Imaging studies characteristically reveals multiple lesions either confined to a single long bone or to an entire lower limb.
FIGURE 20-17 Immunelectrophoregram of the serum from a patient with myeloma. Note that there is an excess of gamma globulin, which is overwhelmingly immunoglobulin A (\(\lambda\)).

<table>
<thead>
<tr>
<th>Serum protein electrophoresis</th>
<th>%</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Albumin</td>
<td>32.3</td>
<td>56.4-71.6</td>
</tr>
<tr>
<td>Alpha-1</td>
<td>3.6</td>
<td>1.9-4.5</td>
</tr>
<tr>
<td>Alpha-2</td>
<td>5.3</td>
<td>7.3-15.0</td>
</tr>
<tr>
<td>Beta</td>
<td>6.8</td>
<td>6.2-11.5</td>
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<tr>
<td>Gamma</td>
<td>52.0</td>
<td>7.8-18.2</td>
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<table>
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<tr>
<td>IgA</td>
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<td>60-340</td>
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<table>
<thead>
<tr>
<th>Immunofixation electrophoresis gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPE IgG IgA IgM k(\lambda)</td>
</tr>
</tbody>
</table>

*Increased IgA-lambda present*

FIGURE 20-18 Collapse of the fifth lumbar vertebra and replacement by a gelatinous, pinkish gray tissue is seen in this gross photograph of the lower spine removed at autopsy from a patient with multiple myeloma.

FIGURE 20-19 Lateral tomogram of L2, with parts of L1 and L3, in a 55-year-old man with multiple myeloma, demonstrating the well-defined lytic lesion, devoid of significant sclerosis, which is characteristic of this disease.
WELL-DIFFERENTIATED ENDOTHELIAL NEOPLASMS

Hemangioendothelioma is a rare locally aggressive tumor that predominantly affects the long bones in adults. Reports of pain or swelling are common. These tumors are osteolytic and may or may not be poorly demarcated on radiographs (Fig. 20-27).
Periosteal new bone formation is unusual in hemangioendotheliomas. Macroscopically, a multiloculate hemorrhagic tumor mass is typically found. (However in epithelioid hemangioendothelioma the lesions are usually solid and gray-white without the hemorrhagic quality characteristic of hemangioma or angiosarcoma.) Microscopically the tumor is characterized by anastomosing cords of vascular channels lined with mildly atypical plump endothelial cells. In some cases, an inflammatory infiltrate is present in which eosinophils may be prominent (Fig. 20-28). Occasionally, the endothelial cells have an epithelioid appearance, which lack pleomorphism or significant mitotic activity. More commonly primary in lung, liver, and soft tissue, this tumor tends to involve bone in a multifocal fashion and with the production of lytic defects.

In this epithelioid tumor, it is often difficult to find vasoformation, and solid foci of polygonal cells in a myxoid stroma may cause diagnostic confusion. Tumor cells have a moderate amount of pink cytoplasm and frequently possess a clear cytoplasmic vacuole representing an intracytoplasmic lumen (Fig. 20-29).

**FIGURE 20-22—CONT’D** B, A computed tomography scan shows an expanding lesion with focal mineralization, which is due to calcified amyloid. C, Photomicrograph of the lesion shows myeloma with foci of smooth, homogeneous pink material (amyloid) (H&E, × 4 obj.). (Courtesy of Dr. Harlan Spjut.)

**FIGURE 20-23** Radiograph of a 40-year-old woman, who reported severe pain in the shoulder, shows a well-demarcated bubbly lytic lesion in the scapula, which, when biopsied, was found to contain only plasma cells.

**FIGURE 20-24** Gross photograph of the knee obtained from a 54-year-old man. At the time of resection, no other evidence of myeloma was present in this patient.
The lining cells express factor VIII–related antigen as well as CD31 and CD34.

Wide resection is the treatment of choice. Although these tumors may recur they rarely, if ever, metastasize.

**POORLY DIFFERENTIATED ENDOTHELIAL NEOPLASMS**

Angiosarcoma is a fully malignant, metastasizing neoplasm that predilects the lower limb and affects adults of all ages, more usually men. These tumors are characterized by rapid growth and extensive bone destruction, with erosion of the cortices and extension into soft tissues. Metastases to the lungs and other organs are common. The lesion consists of irregular, anastomosing vascular channels lined with malignant cells that exhibit prominent intravascular budding and striking cellular anaplasia with frequent mitoses (Fig. 20-30). Solid undifferentiated areas are often present and may suggest a poorly differentiated carcinoma or an anaplastic lymphoma. As with other sarcomas, foci of necrosis are common. Immunoperoxidase staining for factor VIII and other endothelial markers (CD31) may be helpful in some cases.

Radical surgery is the treatment of choice.
Section V
Bone Tumors

Hemangiopericytoma

Hemangiopericytoma is a very rare, low-grade vascular tumor that occasionally occurs as a primary intraosseous lesion. Patients may present with localized pain. Radiographs are nonspecific and may reveal either lysis or focal sclerosis. Gross examination is likely to show a solid tumor.

The intervascular stroma contains typical oval to spindle-shaped mononuclear cells believed to arise from a perivascular precursor cell (the pericyte) with the characteristics of smooth muscle. However, immunohistochemical and ultrastructural studies have generally not found evidence of smooth muscle or pericytic differentiation in these tumors, which therefore may be best classified in the category of fibrous neoplasms (i.e., solitary fibrous tumor).

The key to the diagnosis of hemangiopericytoma is recognition that the neoplastic cells surround the vascular spaces and are not formed from the endothelial lining cells (Fig. 20-31). As with solitary fibrous tumor/hemangiopericytoma of soft tissue, immunostain for CD34 is usually positive at least focally. Because in some cases of mesenchymal chondrosarcoma the predominant pattern may be that of a hemangiopericytoma, it is important to look for...
FIGURE 20-30  

A, Radiograph of the leg of a 70-year-old man with a few months’ history of mild pain. There are several well-defined lytic lesions in the upper diaphysis that are also involving the cortex. 

B, Low-power photomicrograph to demonstrate the erosion of the bone by the tumor (H&E, × 4 obj.). 

C, Higher power photomicrograph to demonstrate numerous vascular spaces lined by large pleomorphic cells, consistent with an angiosarcoma (H&E, × 25 obj.).

(Continued)

FIGURE 20-31  

A, Radiograph of a 30-year-old man with a 1-year history of vague pain in the left arm. A recent acute injury necessitated admission. A well-demarcated lytic lesion of the upper diaphysis with a pathologic fracture is apparent. 

B, Section through the resected segment of the humerus shows a fleshy tumor extending into the soft tissue from the intramedullary space. The opaque yellow infarcted area may be related to a past fracture in this area.
Evidence of cartilage formation when the diagnosis of hemangiopericytoma is being considered. It is important to remember that several other tumors focally show a hemangiopericytoma-like growth pattern (e.g., synovial sarcoma, endometrial stromal sarcoma, melanoma).

Surgery is the treatment of choice; the prognosis is influenced by features such as mitotic rate and necrosis; metastases are more frequent in histologically high-grade tumors.

**Metastatic Cancer**

The most frequent malignant tumor found in the bone is metastatic, and it usually presents with pain. Metastatic disease is considerably more common than a primary bone tumor and should always be considered in the differential diagnosis, even of a solitary lesion. Reflecting the general prevalence of neoplasia in the population, most metastatic bone lesions are from primary carcinoma arising in the breast, prostate, lung, kidney, thyroid, or colon (Figs. 20-32 to 20-34). However, on occasion spindle cell tumors are encountered, for example, leiomyosarcoma usually from the uterus (Fig. 20-35). Because renal cell carcinoma may demonstrate sarcomatous differentiation, it needs to be excluded when one is dealing with a nonmatrix-producing sarcoma of bone.

In young children, metastatic disease is likely to occur from Wilms’ tumor, neuroblastoma, retinoblastoma, and embryonal rhabdomyosarcoma, and needs to be differentiated from a primary Ewing’s tumor and lymphoma.

On imaging studies, the axial skeleton is most frequently involved and the lesions may appear as sclerotic or lytic, solitary, or multiple. Scintigraphy has greatly facilitated the identification of multiple bone metastases, and today the positron emission tomography scan is playing an increasing role in the detection of metastatic disease. In general, whereas purely blastic or sclerotic lesions are seen with prostate and breast carcinoma, kidney and thyroid metastases are destructive and frequently expansile. In the case of osteoblastic metastases, the bone that is formed is reactive and is present as fine spicules of woven bone adherent to the residual existing bone (Fig. 20-36). It is not unusual for patients with an undiagnosed primary tumor (e.g., in the kidney) to present initially with a solitary lytic lesion in the bone, and in such a case, problems of differential diagnosis may arise (Fig. 20-37).

Although in most cases bone metastases present centrally within the medullary cavity, in rare cases they may present as cortical defects. This is often the case with lung carcinoma, which also may present as acral metastases (Fig. 20-38). (The preferential deposition of tumor cells in bone marrow may be explained by the latter's rich vascularity and large sinusoidal channels.)

It should be noted that because bone is a rich source of immobilized growth factors (e.g., fibroblast growth factor, platelet-derived growth factor), which are liberated during resorption associated with tumor expansion, these released factors may then stimulate additional tumor growth.

The diagnosis of metastatic disease is often aided by fine-needle aspiration biopsy. In these circumstances, smears should be made to facilitate the interpretation of fine cytologic detail, and both core bone and blood (clot) should be processed and examined. The blood clot may exhibit evidence of cancer in many cases in which crushed tumor tissue precludes interpretation of the bone sample (Fig. 20-39).

Microscopic identification of the primary site from which the metastasis has originated may be difficult, especially in poorly differentiated neoplasms. Well-differentiated tumors may show squamous pearls, if they are from a squamous carcinoma, and mucin-producing glands, if they stem from an adenocarcinoma. (It should be noted that whereas gastrointestinal adenocarcinomas usually produce mucin, those from the lung may not, and those from the kidney rarely do.) The clear cells of renal cancer may create considerable diagnostic confusion, suggesting a clear cell chondrosarcoma, chordoma, or even liposarcoma. Appropriate immunologic markers are indicated for breast, lung, and so on.
FIGURE 20-33  A, Photomicrograph of metastatic adenocarcinoma, which proved on immunohistochemistry to be from the breast (H&E, × 10 obj.). B, Gross cystic disease fluid protein-15 (BRST-2) is seen running in between the cords of cells (immunoperoxidase, × 10 obj.). C, Estrogen receptor marker is positive on the nuclei (immunoperoxidase, × 25 obj.).

FIGURE 20-34  A 38-year-old man presented with gastric bleeding and back ache with some leg weakness. The magnetic resonance imaging scan (A) shows disc disease at several levels and a totally abnormal marrow signal that was also present in other bones including the pelvis. A biopsy of the iliac bone (B) shows bony erosion and necrosis with replacement of the marrow spaces by spindle cells and myxoid tissue (H&E, × 4 obj.). (Continued)
FIGURE 20-35 A 68-year-old woman presented with pain and swelling of the ankle following trauma. An anteroposterior view of the ankle (A) shows mottled lucency and sclerosis and a biopsy (B) showed a spindle cell tumor consistent with leiomyosarcoma (H&E, × 25 obj.). C, When stained for smooth muscle actin, it was found to be positive. A prior history revealed that 30 years before, uterine fibroids had been removed (immunoperoxidase, × 10 obj.). (Courtesy of Dr. Howard Dorfman.)
Chapter 20
MALIGNANT NONMATRIX-PRODUCING BONE TUMORS

Figure 20-36  A, Scanning electron micrograph of a portion of bone obtained from metastases from an osteoblastic prostatic carcinoma. The fine trabeculae of bone produced in response to the tumor are apparent (× 10 magnification). B, Photomicrograph of the same specimen shows the woven character of the new bone, which is firmly adherent to the surface of the lamellar bone of the vertebral body. The spaces in between are filled with fibrous tissue and malignant cells (H&E, × 10 obj.).

Figure 20-37  Radiograph of an aggressive lesion in the proximal humerus of a 70-year-old man who was in otherwise good health. A primary bone tumor could not be excluded radiographically. The differential would include malignant fibrous histiocytoma, solitary myeloma, and chondrosarcoma. Further investigation revealed a primary carcinoma in the kidney.

Figure 20-38  Radiograph of the middle phalanx of a 60-year-old man who reported pain. Biopsy revealed metastatic carcinoma, which proved to be primary in the lung.
Figure 20-39  A, Photomicrograph of a needle biopsy taken from a vertebral body with a sclerotic lesion suspected of arising from metastatic cancer. There is obviously active new bone formation as well as fibrous scarring, and a clump of atypical cells is strongly suggestive of tumor. Definitive diagnosis may be difficult on this type of tissue (H&E, × 40 obj.). B, Within the aspirated clot, there is clear evidence of adenocarcinoma. Often, in needle biopsies of bone, severe crushing artifacts preclude interpretation of the tissue sample. For this reason, the aspirated blood clot should always be submitted for examination, and will frequently give positive results when the bone tissue sample is negative or equivocal (H&E, × 40 obj.).
Baron Guillaume Dupuytren (October 5, 1777, near Limoges—February 8, 1835, Paris). In 1794, at the age of 18, Dupuytren obtained a post as prosector of the École de Santé, Paris, where he gave anatomy lectures, and was placed in charge of all the autopsies at the medical school. When he was 24, in 1801, he was appointed Chef des travaux anatomiques and soon had written a monograph on pathological anatomy based on his autopsy findings. At the age of 25, he was appointed Chirurgien en second at the Hôtel-Dieu. It was in 1831—some four years before his death—that Dupuytren operated on the contracture that bears his name, after having waited for several years for a suitable subject; the patient was a wine merchant. After eight weeks, the finger had “normal” movements. Of his large fortune he left 200,000 francs to the medical faculty for the establishment of a chair of pathological anatomy. The money was used to found a pathological-anatomical museum instead—the Musée Dupuytren, which still exists in l’Hôpital Cochin, Paris. (From Guillaume Dupuytren. Wikipedia. Available http://en.wikipedia.org/wiki/Guillaume_Dupuytren.)

Arthur Purdy Stout (November 30, 1885, New York City–December 21, 1967, New York City). Stout was educated at Yale University where he received his AB in 1907. After a year spent traveling in Asia, he entered the College of Physicians and Surgeons of Columbia University and received his MD in 1912. He was one of the most prominent pathologists of his era, with a special expertise in tumor pathology. During his tenure as director (1928–1951), the Laboratory of Surgical Pathology at the Columbia-Presbyterian Medical Center gained an international reputation and trained many future leaders in the field. Stout was the author of over 300 scientific articles and he also wrote four fascicles of the Armed Forces Institute of Pathology’s Atlas of Tumor Pathology. He belonged to 16 professional societies and was the recipient of numerous awards. In 1947, an organization of surgical pathologists was named the Arthur Purdy Stout Club in his honor. The name was changed in 1956 to the Arthur Purdy Stout Society of Surgical Pathologists. (Courtesy of the Arthur Purdy Stout Society.)
Benign Synovial Lesions

SYNOVIAL HEMANGIOMA

A synovial hemangioma is a solitary benign lesion, most commonly seen in the knee joints of children and adolescents. These patients may present clinically with a swollen knee associated with mild pain or limitation of movement; occasionally, there is a history of recurrent episodes of pain and joint swelling of several years’ duration.

A soft tissue mass may be evident on imaging studies, although magnetic resonance imaging (MRI) may be necessary to show it clearly. In severe cases, a periosteal reaction or lucent zones in the adjacent bones may also be present.

Gross examination of the resected synovial tissue reveals a soft, doughy mass with overlying villous hyperplastic synovium, which is frequently stained mahogany brown as a result of repeated bleeds. When the mass is viewed microscopically, arborizing vascular channels of different sizes are seen (Fig. 21-1), and in chronic cases with repeated hemarthrosis, copious iron deposition can be observed.

Complete surgical excision may be difficult to effect, and this fact probably accounts for the occasionally reported cases of recurrence.

In Figure 21-2, a capillary hemangioma resected from a tendon sheath of a patient clinically diagnosed as de Quervain’s disease is illustrated.

HOFFA’S DISEASE (LIPOMA ARBORESCENS, VILLOUS LIPOMATOUS PROLIFERATION OF THE SYNOVIIUM)

Hoffa’s disease is a post-traumatic reactive condition of the synovium, clinically most often seen in the knee and characterized by enlargement of the infrapatellar fat pad on either side of the patellar tendon. Rarely, the condition may occur in any joint. The patient usually reports pain or deep aching in the anterior compartment of the knee, which is aggravated by physical activity. A recurrent effusion may be the consequence of repeated synovial injury. The treatment of Hoffa’s disease is surgical reduction in the volume of extrasynovial fat.

When the lesion is examined macroscopically, the synovium has a marked papillary, yellow, fatty appearance; microscopically, there is mild hyperplasia of the synovial lining cells with abundant unremarkable fat extending to the synovial lining. Occasionally, a mild to moderate chronic inflammatory infiltrate may be present (Fig. 21-3).

PRIMARY SYNOVIAL CHONDROMATOSIS

(PRIMARY SYNOVIAL CHONDROMETAPLASIA)

Primary synovial chondromatosis is a rare condition characterized by the proliferation of islands of irregularly hypercellular cartilage in the
synovium of a major joint, often the knee, or, occasionally, in a tendon sheath. Primary synovial chondromatosis needs to be distinguished from the much more commonly observed occurrence of articular cartilage fragments in the synovial tissues of patients following traumatic injury or associated with osteoarthritis (see Chapter 10). The finding of clonal karyotypic abnormalities in synovial chondromatosis casts doubt on the view that this is a reactive process.

Patients with primary synovial chondromatosis have been observed in their second through seventh decades of life, and men appear to be affected about twice as frequently as women. The patients usually...
Section VI  Soft Tissue Tumors

report the gradual onset of pain, stiffness or an enlarging mass around the affected joint. Limitation of motion is a characteristic finding on clinical examination. The knee is most commonly affected, and most other cases present in the hip or elbow. The majority of the remaining cases occur in the tendon sheaths of the hands or feet.

The radiologic signs of this disorder include multiple loose bodies of variable size, many of which show varying degrees of calcification and occasional ossification (Fig. 21-4). However, in a minority of cases, there is no calcification, and in such cases, contrast arthrography or MRI may be necessary to demonstrate the lesions (Fig. 21-5). In some cases of synovial chondromatosis affecting the hip joint, erosion of the bone of the neck of the femur has been observed (Fig. 21-6).

At surgery, there are usually multiple cartilaginous loose bodies, both free in the joint and attached to the synovium (Fig. 21-7). The larger cartilage loose bodies often have a multinodular surface, giving them a mulberry-like appearance.

Microscopic examination reveals discrete nodules of lobulated cartilaginous tissue in the synovium, characterized by cellular crowding with cytologic atypia; many binucleate cells may be present and myxoid areas such that, if seen in an intramedullary lesion, would be considered as chondrosarcoma (Fig. 21-8). This disorder appearance differentiates primary synovial chondromatosis from the much more common secondary cartilaginous loose bodies, which occur in association with osteoarthritis, traumatic arthritis, and osteochondritis dissecans (see discussion in Chapters 10 and 11).

The condition frequently recurs following surgery because of the difficulty of achieving complete excision. Rare cases of malignant degeneration in synovial chondromatosis have been described.
Pigmented Villonodular Synovitis  
(Giant Cell Tumor of Tendon Sheath; Benign Synovial Histiocytoma)

Pigmented villonodular synovitis (PVNS) is a locally aggressive synovial tumor that affects both large joints and tendon sheaths, and that is much more frequently found as a solitary nodule and more rarely as a diffuse multinodular lesion. The most common sites involved are the knees and fingers, but this tumor sometimes occurs in the hip, ankle, foot, or wrist. The lesion is usually painless or only mildly painful; the pain appears to be more severe when the lesion is diffuse throughout a major joint. In general, the condition is confined to a single joint or tendon sheath.

The solitary lesions usually present clinically in the small joints or tendon sheaths of the hands or feet, whereas the multinodular
diffuse form presents clinically in the large joints. (Solitary nodules in large joints, although not uncommon, do not usually result in clinical symptoms, and are discovered incidentally at surgery.)

The radiologic signs of PVNS depend on the site of occurrence. In the finger or toe, only soft tissue swelling may be evident, although cortical bone erosion may occur as seen in Figure 21-9. In the knee, the only consistent radiographic change is soft tissue swelling in and around the joint, which may be massive. In the hip, joint narrowing and lytic defects in the bone may be present on both sides of the joint (Fig. 21-10). Local juxta-articular bone erosion may also be quite

FIGURE 21-8 A, Photomicrograph of the synovium removed from a patient with primary synovial chondromatosis shows irregular nodules of hypercellular cartilage within the synovium (H&E, × 10 obj.). B, Higher power view of primary synovial chondromatosis lesion shows atypical cells that are crowded and clumped. This histologic picture helps to distinguish primary synovial chondromatosis from the secondary chondromatosis that is frequently seen in association with osteoarthritis and trauma (compare this with Figure 10-36) (H&E, × 25 obj.).

FIGURE 21-9 A, Radiograph of the foot in a middle-aged male with a swelling of the second toe shows, in addition to a soft-tissue mass, several intraosseous lytic areas in the middle phalanx. B, Lateral view of the amputated second toe shows a tan tumor enveloping the bone. C, Gross photograph of a section through the specimen. A soft-tissue tumor can be seen extending around and involving the distal interphalangeal joint. The lesion is also invading the medullary cavity of the phalanx. Focally, the tumor has a tan color. D, Photomicrograph of a sagittal section through the toe proved to be PVNS. Tumor tissue is seen both in the soft tissue and invading the bone and joint space. The pinker areas within the tumor tissue represent areas of collagenization (phloxine and tartrazine, × 1 obj.).
Fig. 21-10  A, Radiograph of a young woman with a history of rapid deterioration of function in the left hip shows destructive changes on both sides of the joint, with marked narrowing of the joint space. Because of these radiographic findings, a diagnosis of tuberculosis was considered; however, at surgery abundant hemosiderotic synovium containing nodular fleshy areas was found. B, Cross section of the femoral head, C, reveals dissection of the articular cartilage, with proliferation of soft tissue between the bone and cartilage. D, Specimen radiograph. E, Histologic section of this tissue reveals proliferating mononuclear cells and giant cells in the subchondral bone. A diagnosis of PVNS was confirmed (H&E, x 10 obj.).
prominent in joints such as the wrist, knee, and ankle (Fig. 21-11). MRI and computed tomography are useful to document the extent of the lesion (Fig. 21-12), and on T₁-weighted MRI, the iron deposits may show up as punctate signal voids within the lesion.

On gross examination, the firm whitish lesions tend to have a tan color, which is often more prominent at the periphery, and their texture may vary in firmness depending on how much fibrous tissue they contain. In the tendon sheath of a finger, the lesion is usually solitary and well circumscribed. When the tumor occurs in the knee joint, it is most commonly solitary and it is an incidental finding (Fig. 21-13). In obvious clinical cases of PVNS in a large joint, the lesion commonly consists of multiple nodules, often with dramatic associated hyperplastic villous changes and extensive hemosiderin deposition in the adjacent unaffected synovium (Fig. 21-14).

On microscopic examination, the lesional tissue is localized below the lining cells of the synovial membrane (Fig. 21-15). It is composed of proliferating, collagen-producing polyhedral fibro-histiocytic cells, often with scattered, multinucleated giant cells (Fig. 21-16). Iron deposits and aggregates of foam cells may be present, but these are usually seen in the periphery of the lesion and are most consistent with secondary changes following hemorrhage into the lesion. Abundant production of collagen may be evident in patients with long-standing disease (Fig. 21-17). Occasionally, the cellularity of the lesion, especially when associated with a

**FIGURE 21-11** A, Radiograph of the wrist of a 30-year-old male who presented with swelling and pain in the joint. The lytic defect in the lower radius was due to erosion of the bone by PVNS. B, Lateral radiograph of a knee showing marginal erosions on both sides of the joint in this patient with PVNS.

**FIGURE 21-12** A, Cross sectional CT of the right hand of a patient complaining of a slowly growing mass in the palm. B, Photograph of the removed transected nodule. The nodule was 5 cm across, firm, and on cut section, formed mostly of white tissue with focal areas of yellow tissue, which corresponded to xanthomatous areas microscopically. Pigmentation seemed to be confined to the periphery of the lesion. Pigmentation is often found in lesions of PVNS and probably occurs as a result of secondary hemorrhage into the lesion following trauma.
trabecular pattern of the intercellular matrix, may give a pseudosarcomatous appearance (Fig. 21-18). The lesion is usually non-inflammatory or contains only a sparse scattering of lymphocytes and plasma cells.

At surgery, the differential diagnosis of PVNS includes hemosiderotic synovitis, which is seen in patients with chronic intra-articular bleeding (e.g., in hemophilia and foreign body giant cell reaction following total joint replacement [see Chapters 12 and 14]). Although hemosiderotic synovitis contains a significant amount of pigment, it lacks the distinct submembranous mononuclear and giant cell nodular cell proliferation that characterizes PVNS (Fig. 21-19).

In some cases of rheumatoid arthritis, extensive hemorrhage may lead to hemosiderin deposition and grossly suggest PVNS at surgery (Fig. 21-20). The treatment of PVNS is excision; however, because complete surgical removal is often difficult in diffuse cases, clinical recurrence is fairly frequent.

Genetic studies have shown that tenosynovial PVNS consist of a minority (<20%) of neoplastic cells that harbor rearrangements of the CSF1 gene on chromosome 1p. The majority of cells are non-neoplastic histiocytes that are thought to be recruited to the tumor by cytokines produced by the neoplastic clone. Very rare cases of malignant transformation have been reported.
Under these two designations are a group of rare tumors seen in adults (mean age around 50 years). They occur in women more than men, most commonly seen in the subcutaneous tissues of the foot and ankle, less commonly in the leg, thigh, and rarely elsewhere.

The lesion consists of proliferating spindle cells and histiocytes with varying degrees of pleomorphism but with absent or very low mitotic activity, which is infiltrating adipose tissue; nevertheless, the lesion may be mistaken for a sarcoma. An inflammatory infiltrate and myxoid areas may be noted as well as hyalinized vessels. A striking feature of the lesion is heavy deposits of hemosiderin, which may lead to the mistaken diagnosis of PVNS. Although the lesions have been reported to recur following excision, no cases of metastatic disease have been reported (Fig. 21-21).

**Benign Fibrous Lesions**

Fibrous tumors and tumor-like lesions are common in the soft tissues and tend to be complicated. Some, such as desmoid tumor, look at first sight to be histologically perfectly bland yet are infiltrative lesions that are poorly circumscribed and, therefore, tend to recur repeatedly following excision and may ultimately be lethal depending upon their location.

Others, such as nodular fasciitis, proliferative fasciitis, and proliferative myositis, grow rapidly, are cellular, disorganized, and have a high mitotic rate; they look like sarcomas and yet are self limiting and readily cured by excision.

**FIGURE 21-15** Photomicrograph illustrates a subsynovial focus of PVNS with adjacent uninvolved proliferative synovium (H&E, × 4 obj.).

**PLEOMORPHIC HYALINIZING ANGiectatic TUMOR—HEMOSIDEROTIC FIBROHISTIOCYTIC LIPOMATOUS LESION**

Under these two designations are a group of rare tumors seen in adults (mean age around 50 years). They occur in women more than men, most commonly seen in the subcutaneous tissues of the foot and ankle, less commonly in the leg, thigh, and rarely elsewhere.

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**Benign Fibrous Lesions**

Fibrous tumors and tumor-like lesions are common in the soft tissues and tend to be complicated. Some, such as desmoid tumor, look at first sight to be histologically perfectly bland yet are infiltrative lesions that are poorly circumscribed and, therefore, tend to recur repeatedly following excision and may ultimately be lethal depending upon their location.

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**FIGURE 21-16** A, Low-power photomicrograph of a typical area of pigmented villonodular synovitis demonstrates the nodular accumulation of mononuclear cells with interspersed giant cells, which frequently have peripherally arranged giant cells (H&E, × 4 obj.). B, Higher power shows the typical large stromal histiocytes and giant cells (H&E, × 25 obj.). C, Accumulation of xanthoma cells may on occasion be extensive (H&E, × 10 obj.).
Fibroma of Tendon Sheath

Fibroma of tendon sheath is a distinct entity most commonly seen in the hands and feet. It usually presents as a small, slowly growing mass, which may have been present for many years. Men are more commonly affected and most are adults between the ages of 20 and 50.

Grossly the lesions generally measure less than 2 cm in diameter and have a very circumscribed lobular appearance, which on cut section are firm and gray-white (Fig. 21-22). Microscopically, they are made up of collagen-producing fibroblastic cells with characteristic elongated vascular cleft-like spaces throughout the lesion. Myxoid areas are common. Occasionally, cellular areas with mild atypia are present, and in these areas, there may be a storiform pattern (Fig. 21-23).

Fibromatosis

Under the generic term of the fibromatoses are grouped a number of conditions that are characterized by fibroblastic tissue, which, by its cellularity and capacity to infiltrate surrounding tissue, mimic a low-grade fibrosarcoma. However, these lesions do not metastasize. They may arise in many parts of the body, are classified according to their relationship to fascia (as deep or superficial), and are known by a variety of names (e.g., desmoid tumor, Peyronie's disease). Of particular interest to the orthopaedic surgeon are palmar fibromatosis (Dupuytren's contracture), which is very common, and its plantar equivalent, which is decidedly less common.

**FIGURE 21-17** Photomicrograph to demonstrate collagen production having a pseudo-osseous appearance in PVNS (H&E, x 25 obj.).

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**FIGURE 21-18** A, Photomicrograph of PVNS in which the collagen is seen in a trabeculated pattern with loose pseudoalveolar spaces between. This pattern, together with the heterogeneity of the cells, gives a pseudosarcomatous appearance to the tissue (H&E, x 4 obj.). B, A higher power view to demonstrate the pseudosarcomatous appearance that may be seen in some cases of PVNS (H&E, x 10 obj.). C, Higher power view (H&E, x 25 obj.).
Extra-abdominal Fibromatosis (Aggressive Fibromatosis; Desmoid Tumor)

This is a relatively common tumor seen in young to middle-aged adults. The tumor arises in the connective tissues of the muscles and aponeurosis, most commonly of the shoulder, pelvic girdle, and thigh. Because of its deceptively harmless microscopic appearance, it is unfortunately often mismanaged clinically.

The patient usually presents with a deep-seated, fixed, firm mass that has been evident to the patient for a few weeks or months at the time of presentation. Depending on location, it may be painful.
CHAPTER 21 BENIGN SOFT TISSUE TUMORS 509

FIGURE 21-21 A, Lateral radiograph of foot shows a soft-tissue mass on the dorsal surface overlying the metatarsals. B, Low-power photomicrograph shows admixed fat, proliferating small spindle cells and sclerotic vessels (H&E, × 4 obj.). C, Higher power view shows spindle cells with admixed chronic inflammatory cells and hemosiderin pigment (H&E, × 10 obj.). D, At higher power, a few pleomorphic cells are evident (H&E, × 25 obj.). Hemosiderotic fibrohistiocytic lipomatous lesion has been confused with PVNS in the past. (Courtesy of Dr. Leonard Kahn.)

FIGURE 21-22 A, This fairly well-defined, lobulated nodule measuring 2.8 cm was removed from the index finger of a 41-year-old male. B, The cut surface reveals a firm, fibrous mass.
A, A photomicrograph taken to include the surface of the lesion shows a somewhat disorganized fibrous lesion with patchy areas of hyalinized collagen and compressed vascular channels which are highlighted in B. [A] H&E, × 4 obj.; [B] CD31, × 10 obj. C, Collagenous bundles can be seen coursing through the lesion and there are focal myxoid areas D. [C] and [D], H&E, × 10 obj. E, Foci of atypical cells may be present (H&E, × 25 obj.). F, Staining for macrophages (CD68) shows focally positivity (immunoperoxidase, × 25 obj.). G, Staining for smooth-muscle actin also shows focal positivity (immunoperoxidase, × 25 obj.).
Characteristically, these tumors are grossly poorly circumscribed and infiltrate the surrounding tissue. Cut sections vary from pink to gray-white and from firm to rock hard in consistency. It cannot be sufficiently emphasized that a wide surgical excision is necessary for successful management.

Microscopically the lesion is composed of uniform, elongated spindle cells separated by abundant collagen. Atypia is not a feature of the lesion. These lesions are not encapsulated and at their periphery are found to be invasive into the surrounding muscle and fat. Lesional cells may be myofibroblastic, and the lesion may focally label for smooth muscle actin and desmin (Fig. 21-24).

Because of inadequate marginal excisions, the rate of regrowth is very high and at subsequent reoperation, it may be difficult both for the surgeon and the pathologist to distinguish recurrent tumor from scar tissue (Fig. 21-25).

Desmoid tumors frequently complicate familial adenomatous polyposis and Gardner’s syndrome, and in that setting, the tumors typically demonstrate abnormalities of the FAP gene. In contrast, sporadic desmoids typically show extra copies of chromosomes 8 or 20 and have a high frequency of mutations in the beta-catenin gene. Although immunopositivity for beta-catenin has been suggested as a diagnostic marker for desmoid, it is not specific and frequently labels other fibrous tumors.

Dupuytren’s Contracture (Palmar Fibromatosis)

Palmar fibromatosis usually occurs in older adults and has an incidence of 10% to 20% in the general population. It is three to four times more common in men than in women and is frequently bilateral. It may be familial. In some instances, it is associated with diabetes mellitus as well as epilepsy and alcoholic cirrhosis of the liver.

Patients present with nodular thickening of the palmar fascia (Fig. 21-26) and flexion contracture of the fingers (usually the third, fourth, and fifth).

**FIGURE 21-24** A, An MR image of the right forearm of an 18-year-old male with a recent history of a mass in the forearm. B, A cross-section of the amputated forearm showing the relationship of the mass to the radius and ulna. C, A low-power photomicrograph shows the tumor firmly attached to the adjacent bones (H&E, × 1 obj.).

(Continued)
FIGURE 21-24—CONT’D  

D, A low-power photomicrograph to show the typical appearance of an extra-abdominal desmoid tumor. Interdigitating bundles of fibroblasts with abundant intercellular collagen matrix (H&E, × 4 obj.). E, A higher power photomicrograph to show the bland appearance of the fibroblasts (H&E, × 25 obj.). F and G, Photomicrograph to show collagen bundles of the interosseous membrane entering the cortex with tumor invading the membrane (F] H&E, × 4 obj. [G] same, polarized).

FIGURE 21-25  

A, Radiograph of a 13-year-old girl with a history of two excisions of a desmoid tumor involving the plantar tissue, who was admitted to the hospital because of recurrence with bone involvement. Both soft-tissue swelling and invasion of the second metatarsal bone can be appreciated. B, This amputated specimen with plantar skin removed clearly shows the extent of the tumor.
On histologic examination, the lesions vary in cellularity; some are very cellular and others are heavily collagenized (Figs. 21-27 and 21-28). The cellular lesions are in all probability the more recent, whereas the collagenized lesions have been present for a longer period of time. The cellular lesions are made up of plump, crowded fibroblasts with a variable number of mitoses and this may suggest to the microscopist a fibrosarcoma. However, this diagnosis...
is extremely unlikely in the setting of a typical clinical presentation of Dupuytren’s contracture. Foci of mild chronic inflammation and hemosiderin deposition may be present.

Cytogenetic abnormalities, including trisomy of chromosomes 7 and 8 and loss of the Y chromosome, have been reported.

Plantar Fibromatosis

Plantar fibromatosis is rare in comparison with Dupuytren’s contracture. Like palmar fibromatosis, the incidence of plantar fibromatosis increases with age; however, unlike Dupuytren’s contracture, it also occurs in children, and young and adult patients. It may be present with larger nodules than is usually the case in patients with palmar fibromatosis and generally is not associated with the formation of significant contractures.

Surgical excision is the treatment of choice; however, because of the infiltrative nature of the lesion local recurrence is common.

The microscopic features are similar to those seen in palmar fibromatosis. Because the lesions in the foot tend to be operated on earlier than those in the hand, they appear relatively more cellular; this and the rarity of the condition means that problems in differential diagnosis are more likely to occur in the foot lesions than with Dupuytren’s contracture.

Calcifying Aponeurotic Fibroma (Juvenile Aponeurotic Fibromatosis, Keasbey Tumor)

Calcifying aponeurotic fibroma usually presents as a slowly growing, painless mass commonly in the hands or, less frequently, in the feet of children or young adults. Occasionally, adults may be affected. The mass has usually been present for several months or even years at the time of presentation. Radiographically, calcific stippling may be apparent. Grossly, the lesion is usually an ill-defined, firm, white-gray nodular mass smaller than 3 cm in diameter. Because of calcification, it may have a gritty consistency when sectioned. Microscopic examination shows foci of plump cellular fibroblasts separated by more densely collagenized tissue. Mitotic Figures are rare. Foci of calcification are generally present within the lesion and are usually associated with areas of cartilaginous metaplasia (Fig. 21-29). However, in very young children, calcification may not be evident, making the differentiation
from infantile fibromatosis difficult. In such cases, the location in the fingers or the palm of the hand should suggest the diagnosis.

**NODULAR FASCIITIS**

Nodular fasciitis is a relatively common pseudosarcomatous proliferation of myofibroblasts, which, because of its rapid growth, atypia, cellularity, and mitotic rate, can be mistaken for a malignant condition.

It occurs most frequently in patients between the ages 10 and 40, and is seen most often in subcutaneous tissue on the volar surface of the forearm. Less commonly, it may occur in the head and neck region, the trunk, and on the lower extremity.

In most cases, when the patient is first seen, the lesion has been present for 1 or 2 weeks, and it is usually smaller than 2 cm in diameter and well circumscribed.

Microscopically the lesional tissue is composed of plump immature fibroblasts, having pale nuclei and prominent nucleoli, which in general do not vary from each other. Although mitoses may be frequent, there are no atypical mitoses. The fibroblasts are generally arranged in short irregular interlacing bundles and in addition to a scant collagen matrix, there is generally a focally mucoid matrix. Scattered through the lesion, there are often focal mild inflammatory infiltrates and extravasated red blood cells (Fig. 21-30). Generally, an attachment to the fascia can be found.

Proliferative fasciitis and proliferative myositis are related conditions that tend to occur in an older population than in those with nodular fasciitis, as well as in somewhat different locations; most cases of proliferative fasciitis and proliferative myositis occur in the extremities, whereas most cases of nodular fasciitis occur on the trunk, especially around the chest and shoulder. The histologic features are similar to those seen in nodular fasciitis. It would appear that proliferative fasciitis and myositis are reactive conditions and self-limiting.

Detection of clonal karyotypic abnormalities in nodular fasciitis suggest that this self-limited myofibroblastic proliferation has features of a neoplasm. Furthermore, recurrences are sometimes seen when the lesion is incompletely excised during the active growth phase.

**MYOFIBROMA AND MYOFIBROMATOSIS (INFANTILE MYOFIBROMATOSIS)**

These lesions, which most commonly affect the dermis, may be seen not only in infants but also in children and adults. Although most commonly seen in soft tissue, they may also present in the skeleton as seen in Figure 21-31. They are common around the head and neck and males seem to be predilected. Both solitary and multiple lesions that are confirmed to soft tissue and bone have an excellent prognosis and may regress spontaneously.

Microscopically these lesions have a nodular pattern made up of bundles of plump spindle cells with eosinophilic cytoplasm that are vimentin and actin positive. In some areas of the tumor, there may be more packed spindle cells that have a hemangiopericytoma pattern. Focal hyalinization may be present.
FIGURE 21-30  A, Photograph of a subcutaneous nodule resected from the forearm. The tumor is not well demarcated and appears to be infiltrating the surrounding tissue. B, Photomicrograph of the lesion shows a cellular tumor which seems to be intimately associated with a fascial plane seen in the upper left quadrant of the photograph (H&E, × 4 obj.). C, High-power view to demonstrate the matted arrangement of the fibroblasts. Generally, collagen production is slight in such cases of nodular fasciitis and there is often a loose mucoid appearance to the intercellular matrix (H&E, × 25 obj.). Note also the extravasated red blood cells.

FIGURE 21-31  A, Radiograph of a 5-month-old infant with a slowly growing mass on the head present since shortly after birth. The radiograph suggests a differential diagnosis including epidermoid inclusion cyst, eosinophilic granuloma, or cranial fasciitis. B, The CT scan shows that the lesion is extraosseous and involves the bone by secondary erosion.
ELASTOFIBROMA

Elastofibroma is an uncommon, self-limited lesion found in older adults. With rare exceptions, the lesion occurs in the soft tissue between the rib fascia and the inferior portion of the scapula. On gross examination, the tumor is firm and rubbery in consistency and, although circumscribed, is not encapsulated but rather merges with the surrounding tissue.

On microscopic examination, the lesion is formed of dense collagen and fat, interspersed with eosinophilic globules and fibers. Histochemically and ultrastructurally, these fibers and globules consist of elastin (a fibrous protein) and elastin precursors (Fig. 21-32).

FIGURE 21-31—CONT’D C, Photomicrograph of the tissue from the case illustrated in (A and B). The lesional tissue has a nodular cellular appearance (H&E, × 1 obj.). D, Photomicrograph of a portion of the tumor removed from the patient illustrated in (A to C) shows the typical loose nodular arrangement of spindle cells having an eosinophilic cytoplasm with interspersed cellular matrix rich in proteoglycan (foci of basophilic staining) and sparse collagen. Scattered chronic inflammatory cells are present (H&E, × 4 obj.). E, Higher power photomicrograph illustrates the typical appearance of a myofibroma (H&E, × 10 obj.).

FIGURE 21-32 A, Photograph of a mass, present clinically for several years, excised from the soft tissues overlying the scapula. B, Photomicrograph of a portion of the mass illustrated in (A) to demonstrate the disorderly collagenous matrix and bland cellular appearance of the lesional tissue (H&E, × 25 obj.).
It is generally agreed that the lesion is the result of trauma. Treatment is usually by surgical excision.

**Peripheral Nerve Lesions**

**TRAUMATIC (AMPUTATION) NEUROMA**

A traumatic neuroma is an exuberant but non-neoplastic proliferation of nerve tissue resulting from a lacerating injury (often surgery). Clinically, it presents as a firm nodule that is occasionally tender or painful.

Grossly the lesions are circumscribed, white-gray nodules located in continuity with the proximal end of the injured or transected nerve. Microscopically, they consist of a haphazard proliferation of interdigitating nerve fascicles within scar tissue (Fig. 21-33).

Rarely, these lesions may be difficult for the microscopist to differentiate from neurofibromas, especially if there is myxoid degeneration.
Morton’s Neuroma

Morton's neuroma is a distinct clinicopathologic entity characterized by thickening and degeneration of one of the interdigital nerves of the foot, most commonly that between the third and fourth metatarsal heads. The patient, usually a woman, experiences sharp shooting pains that are worse when standing. These pains characteristically begin in the sole of the foot and radiate to the exterior surface. At surgery, a fusiform swelling proximal to the bifurcation of the plantar interdigital nerve is usually seen. When dissected, the resected specimen usually includes the neurovascular bundle (Fig. 21-34).

Histologic sections show three characteristic microscopic features: (1) endarterial thickening of the digital artery, often with thrombosis and occlusion of the lumen; (2) extensive fibrosis both around and within the nerve giving rise to demyelination and a marked depletion of axons within the digital nerve; and (3) evidence of Schwann cell and fibroblast proliferation (Figs. 21-35 and 21-36). The histologic findings are most consistent with recurrent nerve trauma, most probably resulting from the wearing of poorly fitting shoes.

Morton's neuroma should be differentiated from an amputation (traumatic) neuroma, which may also occur in the interdigital nerves of the feet, although very much more rarely.

**FIGURE 21-34** Gross photograph of a segment of the plantar interdigital nerve resected from the space between the third and fourth metatarsal heads in a patient with Morton’s neuroma shows fusiform swelling of the neurovascular bundle just proximal to the bifurcation.

**FIGURE 21-35** A, Schematic diagram of a normal neurovascular bundle illustrating the relationship of the digital nerves and artery. B, Schematic diagram of the neurovascular bundle from a patient with Morton’s neuroma. Note the increased fibrosis in the epineurium, perineurium, and endoneurium. In addition, there is marked endothelial thickening of the artery, with narrowing of the lumen.
Neurilemoma (Benign Schwannoma)

Neurilemoma is an encapsulated nerve sheath tumor that consists histologically of two components: (1) a highly ordered cellular component (Antoni A area) and (2) a loose myxoid component (Antoni B area).

Neurilemomas occur at all ages but are relatively common in persons of both sexes between the ages of 20 and 50 years. They have a predilection for the head, neck, and flexor surfaces of the upper and lower extremities. They almost always occur as solitary lesions, except in patients with neurofibromatosis type 2 (NF2), in whom multiple tumors (especially bilateral schwannomas of the vestibular nerves) are common. Multiple tumors may also be seen sporadically in schwannomatosis. They grow slowly and usually have been present several years before diagnosis is made.

Grossly, these are encapsulated tumors, which in small nerves may have globoid or fusiform shape, and in larger nerves may present as eccentric masses over which the nerve fibers are splayed. On cut section, the tumor is soft and has a pink, white, or yellow appearance. It usually measures less than 5 cm and occasionally has foci of cystification or calcification (Fig. 21-37).

Microscopically, the hallmark of a neurilemoma is the pattern of alternating Antoni A and B areas of varying amounts. Antoni A areas are composed of compact spindle cells that are arranged in short bundles with nuclear palisading or interlacing fascicles of whorling cells. Antoni B areas are far less cellular; the spindled or oval cells are arranged haphazardly within the loosely textured matrix, which is punctuated by microcystic change, inflammatory cells, and delicate collagen fibers. Diffuse and intense immunostaining for S100 protein is seen in the cells (Fig. 21-38). About 60% of schwannomas show mutations in the NF2 gene, which encodes merlin (schwannomin), and virtually 100% of schwannomas fail to express this protein, which is present in normal schwann cells.

Solitary Neurofibroma

The vast majority of neurofibromas are solitary lesions. Multiple neurofibromas, (neurofibromatosis or von Recklinghausen’s disease) are decidedly less common (Fig. 21-39). Neurofibroma differs from neurilemoma in not being encapsulated, although it generally appears to be a circumscribed lesion.

Clinically, most present in patients between 20 and 30 years of age. These are superficial painless lesions seen in the soft tissue, sometimes without evidence of an origin from a peripheral nerve. Grossly, they are firm, translucent white-gray tumors that may be formed of a fusiform expansion around an affected nerve.

Microscopically, the neurofibroma varies, depending on the ratio of cells, mucin, and collagen. Most commonly, it shows interlacing bundles of elongated cells with wavy, dark-staining nuclei with intercellular wire-like strands of collagen and small to moderate amounts of mucoid material that separate the cells and collagen. The criss-crossing collagen bundles are often likened to shredded carrots. The stroma of the tumor is dotted with occasional mast cells and lymphocytes (Fig. 21-40). Generally, the S100 stain is much less intense than in neurilemoma. Unlike schwannomas (which are
composed solely of neoplastic Schwann cells), neurofibromas consist of a heterogeneous population of Schwann, perineurial-like, and fibroblastic cells.

Neurofibromatosis type 1 associated neurofibromas include clonal proliferations of Schwann cells showing abnormalities at the NF1 locus. However, because of their heterogeneous cellular composition, it has been more difficult to study the genetics of the more common sporadic neurofibromas.

**Miscellaneous Lesions**

**LIPOMA**

Benign fatty tumors are the most common soft tissue tumors and come in a wide variety. The fatty tissue may be admixed with vascular tissue (angiolipoma), muscle tissue (myolipoma), cartilage tissue (chondrolipoma), or be a mixture of any of these elements (Figs. 21-41 and 21-42). Occasionally, calcification or ossification may be seen in a lipoma. A subcutaneous location is the most common, but lipomas may also appear in muscles, tendon sheaths, nerves, and joints.

Neural lipomas may be associated with a fibrolipomatosis hamartoma and macrodactyly (Fig. 21-43), which usually presents in childhood as an isolated lesion. In its extreme form—Proteus syndrome—fibrolipomatous hamartoma is responsible for causing the deformities seen in the elephant man.

Lipomas are rarely seen in young people and clinically usually present in patients older than 40 years of age. They appear to be somewhat more common in men and are occasionally multiple. Most lipomas are superficial in location, and present on the trunk and the proximal portions of the extremities. Deep lipomas are decidedly rarer and, therefore, often present more of a problem in diagnosis.

Grossly, soft tissue lipomas are generally well-circumscribed, soft, yellow tumors measuring between 4 to 10 cm in diameter (Fig. 21-44). Microscopically, they normally do not significantly
differ from the surrounding fat, although they are usually lobulated and may have admixed fibrous, myxoid, or other connective tissue elements. Secondary changes such as hemorrhage, infarction, and calcification are not unusual and rests of foamy macrophages are common. Occasionally, atypical cells may result in confusion with liposarcoma especially in pleomorphic lipoma of the back and shoulder region commonly seen in older men.

Lipomas characteristically show translocations, deletions, or other rearrangements involving chromosomes 12p, 6p, or 13q, and the demonstration of these karyotypic abnormalities helps exclude the diagnosis of liposarcoma in difficult cases.

HEMANGIOMA

Hemangiomas are the most common tumors seen in infancy and childhood, and are usually superficial lesions with a predilection for the head and neck region. The majority have a capillary pattern and are composed of small nodules of capillary-sized vessels lined by flattened
to plump endothelium, the nodules being clumped in a lobular pattern (Fig. 21-45). In some cases, the vascular nature of the lesion may be obscured by the plumpness of the endothelial cells, giving a solid appearance to the tumor. In these instances, immunohistochemistry using a vascular marker such as CD 31 can be most helpful.

Cavernous hemangiomas are less common, are usually larger in size than capillary hemangiomas and frequently involve deep structures such as muscles (Fig. 21-46). On radiographs it is sometimes possible to visualize calcified thrombi with a long curvilinear pattern, or more typically with a nodular pattern (phleboliths).
Sometimes multiple hemangiomas are seen in association with multiple enchondromatosis (Maffucci’s syndrome, see Chapter 17) (Fig. 21-47).

Epithelioid hemangioma is a rare but distinctive variety of hemangioma characterized by inflammatory cells, particularly eosinophils, and in addition, plasma cells, mast cells, and lymphocytes. The cells lining the vessels have an epithelioid appearance with eosinophilic cytoplasm and frequently appear as a line of tombstones (Fig. 21-48). The same tumor also occurs in bone with a lower frequency.

Another common painful tumor of the extremities in middle-aged persons is an angiomyoma, which is illustrated in Figure 21-49.
FIGURE 21-47 A, Lateral radiograph of a foot. There are many calcified nodules of approximately the same size in the soft tissues, which represent calcified phleboliths in an extensive soft-tissue hemangioma in a patient with Maffucci’s syndrome. B, Photograph of a resected hemangioma to demonstrate in situ phleboliths.

FIGURE 21-48 A, Photomicrograph of an epithelioid hemangioma to demonstrate the packed and solid appearance of the tumor due to the compression of the vascular spaces (H&E, × 4 obj.). B, At a higher power some of the vascular space can be discerned (H&E, × 25 obj.).

MYOSITIS OSSIFICANS

The diagnostic term myositis ossificans includes two entirely different clinical diseases: fibrodysplasia (myositis) ossificans progressiva and myositis ossificans circumscripta.

Fibrodysplasia (Myositis) Ossificans Progressiva

Fibrodysplasia ossificans progressiva is a rare progressive disease in which groups of muscles, tendons, and ligaments (usually the muscles of the back and those around major joints of the upper limb)
become progressively fibrosed, calcified, and ossified, thereby producing severe functional disability (Fig. 21-50). The disorder is often associated with symmetrical malformation or absence of the digits of the hands and feet. The sexes are equally affected, and there is no racial predilection. The disorder is usually fatal because of progressive functional disability, including impairment of pulmonary function. Symptoms of the disease usually begin in childhood, generally before the age of 10 years.

In some cases, the condition is inherited, and several members of a family may be affected. In most instances, however, it is probably the result of a spontaneous mutation. It is thought that the underlying defect in this condition is a point mutation in a “metamorphogene” encoding bone morphogenetic protein type I receptor (activin receptor 1A/activin-like kinase 2), which regulates the metamorphosis of fibrous tissue into bone during embryogenesis and in the formation of heterotopic bone.

Microscopic examination of the early lesions, which consist of nodular swellings in the muscles and subcutis, reveal a loose proliferation of fibroblasts and interstitial edema that may be confused with a desmoid tumor. Microscopic examination of advanced lesions reveals poorly organized bone (both lamellar and woven), dense, fibrous scar tissue, and islands of poorly formed cartilage (Fig. 21-51).

**Myositis Ossificans Circumscripta**

Myositis ossificans circumscripta is a solitary, nonprogressive, benign ossifying lesion of soft tissues. The patient is usually an athletic adolescent or young adult who presents with a lump in a muscle that has been evident for some weeks and may have been somewhat painful. A history of trauma can usually be elicited, but these traumatic incidents are, more often than not, trivial in nature. A radiograph taken soon after the onset of symptoms may not reveal any calcification, but within 1 to 2 weeks, a poorly defined area of opacification appears. Over the following weeks, the periphery of this shadow becomes increasingly well delineated from the surrounding soft tissue (Fig. 21-52). (Diagnostic problems in such cases occur when the lesion is biopsied in the early phase before peripheral maturation has occurred.)

Gross examination of a focus of myositis ossificans circumscripta that has been present for a month or two reveals a shell of bony tissue with a soft reddish brown central area. The lesion is usually 2 to 5 cm in diameter and is adherent to the surrounding muscle.

Microscopic examination of myositis ossificans circumscripta reveals in the center of the lesion an irregular mass of active, immature myofibroblastic cells, with foci of interstitial hemorrhages that are rarely extensive. This tissue closely resembles nodular fascitis. At some distance from the center of the lesion, depending on the age of the entity in question, small foci of osteoid production can be seen. The resulting tissue may be disorganized and hypercellular. Near the periphery, more and more clearly defined trabeculae are evident. The bone is usually of the immature woven type, with large, round, and crowded osteocytes; however, in long-standing lesions, the bone may be mature and have a lamellar pattern and a fatty/hematopoietic marrow (Fig. 21-53).

Especially in its acute stage, it may be difficult on the basis of histologic evidence alone to differentiate a focus of myositis from a sarcoma. Therefore, careful correlation of the clinical and radiologic findings is essential. An important distinction to be emphasized is that whereas myositis ossificans is most mature at its periphery and least mature at its center, the opposite is true of a malignant tumor (see discussion of soft tissue osteosarcoma in Chapter 22). Treatment of myositis ossificans is usually conservative, with the option of excision of the mass.

A recent X-inactivation study of myositis ossificans circumscripta found evidence of polyclonality, supporting the reactive, reparative nature of this process.

(Three conditions that appear to be related to myositis ossificans circumsripta—subungual exostosis, reactive periostitis, and bizarre parosteal osteochondromatous proliferation—have already been discussed in Chapter 16.)

**SOFT TISSUE CHONDROMA**

Cartilaginous lesions in soft tissues are rare. Most soft tissue chondromas have been described in the hands or feet of patients 30 to 60 years of age. In general, the lesions measure between 1 and 2 cm in diameter, and about one third of the lesions are densely calcified on radiographic examination.

Grossly, the lesions are usually firmly adhered to adjacent structures, tendons, tendon sheaths, or joint capsules, and have a hard, often gritty, consistency. Microscopic examination shows considerable variation. Some consist of mature hyaline cartilage arranged in a lobular pattern. Others show, in addition to the cartilage, areas of fibrosis, myxoid change, or hemorrhage. About one third reveal heavy granular calcification, which may obscure the chondrocytes and suggest the diagnosis of tumoral calcinosis (Fig. 21-54). In many of these latter cases, foci of reactive epithelioid histiocytes and multinucleated giant cells further complicate the histologic presentation. Because of the variable and sometimes bizarre appearance these lesions may be occasionally mistaken for chondrosarcoma, especially if they have a myxoid stroma. (The differential diagnosis should also include primary synovial chondromatosis and tophaceous pseudogout.)
FIGURE 21-50 (A to D) These photographs demonstrate severe deformities of the limbs, spine, and neck, resulting from myositis ossificans progressiva. (E to G) Clinical radiographs of the patient in (A to D) show ossification around both shoulder joints as well as in the paravertebral area and hip.

FIGURE 21-51 A, Photomicrograph of a portion of ossified soft tissue taken from the hip joint of a patient with myositis ossificans progressiva demonstrates both immature bone and cartilage formation, with areas of dense fibrous connective tissue also in evidence (H&E, × 1 obj.). B, Higher power photomicrograph of the tissue in (A) shows bone and cartilage formation within the soft tissue (H&E, × 10 obj.).
FIGURE 21-52  

A, Clinical radiograph of a young woman who developed pain in the region of the pubis after childbirth reveals no obvious abnormality.  
B, Radiograph of the patient in (A), taken 1 month later, demonstrates a well-defined ossifying mass in the soft tissue adjacent to the pubis.

FIGURE 21-53  

A, Gross photograph of the specimen removed from the patient in Figure 21-52. In the upper part can be seen a segment of normal bone pubic ramus, and immediately underlying this segment is a well-circumscribed ossified mass, which, though attached to the periosteum, did not arise from the bone tissue.  
B, Photomicrograph of a section through an intact specimen of myositis ossificans circumscripta clearly shows the fibrous cellular center and the limiting outer layer of more mature bone (H&E, × 1 obj.).  
C, High-power photomicrograph of tissue taken from the center of the mass shown in (A) demonstrates a spindle-cell lesion. The cells have a disorderly arrangement and are producing collagen (H&E, × 25 obj.).
FIGURE 21-53—CONT’D D, Photomicrograph of an area adjacent to the tissue seen in (C) demonstrates immature bone matrix formation. The cellularity of this tissue might cause concern and lead to an erroneous diagnosis of sarcoma (H&E, × 10 obj.). E, Histologic section taken from the periphery of the lesion demonstrated in the previous figures shows mature bone formation, characteristic of myositis ossificans circumscripta (H&E, × 4 obj.).

FIGURE 21-54 A, Radiograph showing a heavily calcified tumor on the volar aspect of a proximal phalanx. Note the punctate appearance of the calcification. B, Photomicrograph of a peripheral field of the tumor to demonstrate viable cartilage and a delicate lace-like pattern of calcification around some of the cells (H&E, × 25 obj.). C, Photomicrograph of a portion of the periphery of the lesion illustrated in (A) shows heavy calcified cartilage with only a few viable chondrocytes at the periphery, consistent with soft-tissue chondroma (H&E, × 10 obj.).

SOFT TISSUE GIANT CELL TUMOR

These rare lesions seem to most commonly occur in the superficial or deep soft tissue of the hand or arm (Fig. 21-55). Microscopically they are similar to giant cell tumor of bone and have a similar immunophenotypic profile.

They may need to be distinguished from nodular tenosynovitis (giant cell tumor of tendon sheath). However, usually their location is different and, as with conventional giant cell tumor of bone, also they lack heterogeneity, which is the hallmark of nodular tenosynovitis. Metaplastic bone may be present usually at the periphery of the lesion.
FIGURE 21-55  A, Radiograph of the long finger of an 83-year-old male complaining of a lump that was increasing in size. The image shows destructive changes in the proximal and distal interphalangeal joints and a large soft-tissue mass adjacent to the proximal joint. B, Photomicrograph of tissue obtained from the resected soft-tissue mass shows a tumor composed of closely packed giant cells separated by mononuclear stromal cells and indistinguishable from a giant-cell tumor of bone (H&E, × 4 obj.). C, Higher power view (H&E, × 10 obj.). D, At the periphery of the lesion there is reactive bone formation (H&E, × 4 obj.).

GANGLION

A ganglion is a fibrous-walled cyst filled with clear mucinous fluid and usually lacking a recognizable lining of differentiated cells (Fig. 21-56).

On microscopic examination, the wall of a ganglion cyst is formed of dense, collagenized fibrous tissue, often with foci of myxoid tissue (Fig. 21-57). Chronic inflammatory cells may be observed, especially if the cyst has been previously ruptured.

Ganglia occur in the soft tissues, usually dissecting between tendon planes. They are often seen in the hands and feet, particularly on the extensor surfaces near joints. (The most common location is around the wrist joint.)

Ganglia may arise either as herniations of the synovium or from cystification of foci of myxoid degeneration within dense fibrous connective tissue, possibly secondary to trauma. Rarely, a communication with the joint cavity can be demonstrated. Evidence from imaging studies has shown that ganglion arising in the peroneal nerve may be related to degenerative changes in (and may communicate with) the adjacent tibiofibular joint.

On occasion, these lesions may erode the adjacent bone and subsequently become totally intraosseous. The most common site for such an intraosseous ganglion is the medial malleolus of the tibia (see Chapter 19). Ganglia are often seen in the parameniscal tissue of the knee joint, usually in proximity to the lateral meniscus (Figs. 21-58 and 21-59). Synovial cysts may also develop in the vertebral column, where they may result in pressure on the nerve root or on the spinal canal contents (Fig. 21-60).

If clinically troublesome, surgical excision of the cyst is the treatment of choice.
**FIGURE 21-56**  
A, Gross photograph of an intact, excised ganglion cyst. Note the smooth fibrous wall and the translucent appearance. B, Gross photograph of a bisected ganglion shows a multiloculated cyst filled with clear glairy fluid. C, Photomicrograph of a ganglion shows the dense fibrous multiloculated connective-tissue wall, with a thin layer of flattened cells lining the cyst (H&E, × 10 obj.).

**FIGURE 21-57**  
Photomicrograph of a portion of the wall of a ganglion showing extensive myxoid change (H&E, × 10 obj.).

**FIGURE 21-58**  
Gross photograph of the lateral meniscus (left) and a parameniscal cyst (right). As is apparent here, cysts of the lateral meniscus may occasionally grow to a very large size.
FIGURE 21-59  

A, Photograph of a portion of the lateral meniscus with a section through an attached cyst. B, Photomicrograph of a cross-section of the lateral meniscus shows focal cystic degeneration in the outer third of the meniscus. Microscopic foci of myxoid degeneration and cystification are common findings in histologic sections of the meniscus (H&E, × 4 obj.).

FIGURE 21-60  Photograph of a ganglion cyst with a portion of the lamina bone taken from the lumbar spine of a patient with symptoms of nerve root compression.
Hugh Owen Thomas* (Liverpool, 1834–1891). Thomas trained for a few years with his uncle, Dr. Owen Roberts, in North Wales and then continued his training in Edinburgh and University College London. He qualified as a member of the Royal College of Surgeons in 1857 at the age of 23. He returned to Liverpool and for a short time practiced with his father, an unqualified bone setter, but two years later set up his own practice from his home, No. 11 Nelson Street. He is regarded now as the father of orthopaedic surgery in the United Kingdom. At the Liverpool Medical Institute (founded 1779), a collection of memorabilia relating to Hugh Owen Thomas may be found. (From Hugh Owen Thomas. Wikipedia. Available at http://en.wikipedia.org/wiki/Hugh_Owen_Thomas.)

Virgil Pendleton Gibney (1847–1927).* Born September 1847 on a farm in Kentucky, Gibney studied medicine at Bellevue Medical College in New York, receiving his MD degree in 1871. His first appointment was at the then new hospital for the Ruptured and Crippled (now the Hospital for Special Surgery) in New York City. In 1887 he was visiting Europe and became good friends with Hugh Owen Thomas, staying at his home, where he also became acquainted with his nephew Sir Robert Jones, who was to become one of the great early orthopaedic surgeons in England. It was during the first world war that a number of American surgeons went to work with Robert Jones in the Center for Special Surgery, which he had set up to treat the wounded. Gibney was the second Surgeon-in-Chief at the Hospital for the Ruptured and Crippled. He died in 1927. (Courtesy of Dr. David Levine.)

* Although neither of these men were pathologists, they certainly have played an indirect role in my life. I went to Liverpool University Medical School where I determined to be a pathologist with an interest in bone and joint disease. Eventually I came to work at the Hospital for Special Surgery (the old Ruptured and Crippled) where I have spent 40 happy years of my professional life.
To put things into perspective, although malignant tumors arising in the soft connective tissues are about three times more common than those arising in the skeletal tissues, they are still 20 times less common than lung cancer.

The most common soft tissue sarcomas are malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, and synovial sarcoma.

Because soft tissue sarcomas tend to show considerable variation in their histologic patterns and can be very difficult to diagnose, it is often wise to seek a second opinion from some authority in the subject.

**Malignant Fibrous Histiocytoma**

The commonest manifestation of malignant fibrous histiocytoma (MFH) is a poorly differentiated pleomorphic high-grade tumor that is characterized by a storiform, matted, or pinwheel pattern and is generally seen in older adults. The microscopic diagnosis is one of exclusion and should not be made until a panel of immunohistochemical and appropriate genetic studies have been performed to exclude other types of sarcoma as well as poorly differentiated melanoma or carcinoma.

The term MFH was first introduced in 1963, and before that time, most of these lesions would have been diagnosed as pleomorphic rhabdomyosarcoma or fibrosarcoma. Today some experts discourage use of the term MFH on the grounds that this tumor lacks true histiocytic differentiation and that widespread use of this diagnostic category may discourage additional studies that would lead to classification as a differentiated sarcoma subtype.

Most of the patients are in the fifth to seventh decades of life, and two thirds are men. The tumor is most often seen in the lower extremity, particularly the thigh, and at the initial presentation has usually been present for several months or even a year or two. Most of the lesions are intramuscular. Occasionally, an MFH may arise in a previously irradiated area.

Grossly the tumor is generally a lobulated, fleshy gray-white mass, between 5 and 10 cm in diameter, which appears circumscribed, even though microscopically, it may have infiltrated into the surrounding tissue and along fascial planes (Fig. 22-1). Occasionally there may be evidence of extensive necrosis and/or hemorrhage. About 20% of these tumors have a decidedly myxoid appearance, which may grossly suggest a myxoid liposarcoma.

Microscopically, MFHs are variable. Most of them have a storiform pleomorphic pattern, and the rest show either a myxoid or a predominantly giant cell pattern, with an inflammatory infiltration both of acute and chronic inflammatory cells, which tend to obscure the underlying tumor.

In the classic storiform-pleomorphic pattern, plump spindle cells are arranged in a matted pattern of short fascicles. Focally, there are large atypical cells, many of them multinucleate giant cells, together with many mitotic figures both typical and atypical (Fig. 22-2).

As already stated, the diagnosis depends on careful exclusion of other entities by the use of immunohistochemistry. Genetic studies typically reveal complex abnormal karyotypes with structural and numerical aberrations.
Liposarcoma

Liposarcomas most often present in the deep soft tissue of the lower extremity, particularly the thigh or in the retroperitoneum. They tend to occur in older adults and are frequently large at the time of clinical presentation.

There are five subtypes of liposarcoma, which can be conveniently grouped into three. The subtypes are distinct from each other histologically, biologically, and cytogenetically (Table 22-1).

Well-differentiated liposarcomas are large multilobular yellow tumors with varying amounts of fibrous tissue coursing through them (Fig. 22-3). Microscopically, the well-differentiated liposarcomas are formed predominantly of mature fat with varying numbers of atypical spindle cells with hypochromatic nuclei and vacuolated lipoblasts; varying degrees of fibrosis and chronic inflammation may be present (Fig. 22-4). Dedifferentiation occurs in around 6% of the extremity lesions but is somewhat more commonly seen in retroperitoneal lesions. The dedifferentiated areas most often have the pattern of an MFH or high-grade fibrosarcoma (Fig. 22-5). Dedifferentiation of a well-differentiated liposarcoma needs to be distinguished from an ab initio pleomorphic liposarcoma (Fig. 22-6).

Myxoid or round cell liposarcomas are also generally large lobular tumors but with a grayish myxoid gross appearance with more solid areas depending on the proportion of the tumor having a round cell pattern. Microscopically, myxoid liposarcomas are multinodular, with each nodule generally paucicellular in the central area and

<table>
<thead>
<tr>
<th>Groups (Frequency)</th>
<th>Subtypes</th>
<th>Age (Years)</th>
<th>Cytogenetics</th>
<th>Recurrence and Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (40%)</td>
<td>Well-differentiated liposarcoma</td>
<td>50–70</td>
<td>Giant and ring chromosomes derived from 12q</td>
<td>Recurrence is more common in retroperitoneal tissue</td>
</tr>
<tr>
<td></td>
<td>Well-differentiated liposarcoma with dedifferentiation</td>
<td></td>
<td></td>
<td>41% local recurrence 17% metastasize</td>
</tr>
<tr>
<td>2 (50%)</td>
<td>Myxoid liposarcoma</td>
<td>25–45</td>
<td>Reciprocal translocation between chromosomes 12 and 16 or 12 and 22</td>
<td>Predominantly myxoid tumors 23% metastasizes</td>
</tr>
<tr>
<td></td>
<td>Round cell liposarcoma</td>
<td></td>
<td></td>
<td>When round cells exceed 25% of the tumor, 58% metastasize</td>
</tr>
<tr>
<td>3 (10%)</td>
<td>Pleomorphic liposarcoma</td>
<td>50–70</td>
<td>Complex abnormal karyotypes</td>
<td>Increased rate of fatality with this pattern</td>
</tr>
</tbody>
</table>
more cellular at the periphery; characteristically, there is a delicate plexiform capillary network coursing through the tumor. The cells are bland and fusiform, and in a myxoid matrix of hyaluronic acid (Fig. 22-7). In the more solid round cell areas, the cells are more closely packed; however, lipoblasts can usually be readily recognized (Fig. 22-8). Occasionally, as in other forms of liposarcoma, immunohistochemical stains demonstrate occasional myoblastic cells as well as keratin positive cells. Tumor cells (lipoblasts) are usually S-100 positive. As in lipomas, occasionally foci of cartilage or bone may be present within a liposarcoma (Fig. 22-9).

FIGURE 22-5 A, This low-power photomicrograph of a dedifferentiated myxoid liposarcoma shows the low grade myxoid liposarcoma (left) and the dedifferentiated cellular tumor (right) (H&E, × 1 obj.). B, Higher power of the low grade myxoid tumor. Note the numerous capillaries coursing through the tumor (H&E, × 10 obj.). C, Photomicrograph of the cellular spindle cell dedifferentiated tumor, which also shows reactive bone formation (H&E, × 10 obj.).

FIGURE 22-6 A, Photograph of a pleomorphic liposarcoma in section. The tumor is surrounded by subcutaneous fat and lies just below the skin. Note how well the tumor is demarcated from the surrounding tissue. B, Photomicrograph to demonstrate the pattern in a pleomorphic liposarcoma (H&E, × 4 obj.).
Rhabdomyosarcoma is a malignant tumor differentiating toward skeletal muscle and is the most common soft tissue sarcoma of children and, to a lesser extent, young adults. It is rare in people older than 40 years of age (Fig. 22-10).

Rhabdomyosarcomas have considerable histologic heterogeneity depending on cellularity, pattern of growth, and cellular differentiation. Generally, they are classified as embryonal (botryoid or spindle cell variants of embryonal), alveolar, or pleomorphic. The botryoid and spindle cell variants of embryonal rhabdomyosarcoma have the best prognosis; those with conventional embryonal rhabdomyosarcoma have an intermediate prognosis, and those with an alveolar or undifferentiated pattern have a poor prognosis.

Embryonal rhabdomyosarcoma with its botryoid and spindle cell subtypes affects mainly children between birth and 15 years of age. Alveolar rhabdomyosarcoma affects a somewhat older age group between the ages of 10 and 25. Pleomorphic sarcomas are rare and seen in patients older than 45 years of age. Most embryonal tumors occur in the head and neck or trunk, commonly around the orbit or the paratesticular region. Many of the alveolar and the rare pleomorphic type occur in the extremities.

Embryonal rhabdomyosarcoma resembles microscopically the various stages of muscle development from poorly differentiated monotonous round cell tumors to well-differentiated tumor cells, with cross-striations resembling rhabdomyoblasts (Fig. 22-11).

In the case of poorly differentiated embryonal tumors, it may be difficult without immunohistochemical staining to distinguish between Ewing’s tumor, neuroblastoma, melanoma, or rhabdomyosarcoma.
Alveolar rhabdomyosarcoma resembles a poorly differentiated embryonal rhabdomyosarcoma but with poorly defined aggregates of round cells separated by vascularized dense fibrous septae. Frequently, the cells in the center of these aggregates show loss of cohesion, resulting in an alveolar pattern (Fig. 22-12).

The most useful immunohistochemical stains for the diagnosis of the rhabdomyosarcoma are desmin, muscle-specific actin, and myogenin. Cytogenetic abnormalities of embryonal and alveolar rhabdomyosarcoma are distinct.

Embryonal sarcomas are characterized by a consistent loss of heterozygosity for multiple closely linked loci at chromosome 11p15.5. Trisomy 8 has also been reported. Most alveolar rhabdomyosarcomas have t(2;13)(q35:14) or t(1;13)(p36;q14) translocation.
Synovial Sarcoma

Synovial sarcomas are rare malignant neoplasms of unknown histogenesis, affecting the extremities, most commonly the lower extremities. Most involve soft tissue in the vicinity of joints, especially the knee. Although the name implies an origin from synovial lining cells, intra-articular synovial sarcomas are decidedly rare. Usually sharply circumscribed, these tumors may extend along fascial planes and/or invade bone.

Both biphasic and monophasic types of synovial sarcoma are recognized. The classic biphasic type has both a spindle cell and an epithelial component. A monophasic spindle cell tumor requires positive immunohistochemical or cytogenetic identification.

Patients with synovial sarcoma usually present between the ages of 15 and 40 years with pain or with a slow-growing mass. The tumor is decidedly rare in children. A lobulated soft tissue shadow may be seen on radiographs, and irregular, spotty calcification is evident in about 20% of affected individuals (Figs. 22-13 and 22-14). Although the lesion may grossly appear to be encapsulated, on microscopic examination, it usually exhibits diffuse infiltration of the surrounding tissues. On gross examination, the tumor has a rubbery consistency and may contain evidence of hemorrhage, cysts, and calcification (Fig. 22-15).

On microscopic examination, classic synovial sarcoma has a biphasic pattern of plump uniform spindle cells and well-differentiated cuboidal to columnar cells forming gland-like spaces, in which cytokeratin and epithelial membrane antigen can be demonstrated (Fig. 22-16). The glandular zones contain mucus-like material that stains positively with periodic acid–Schiff stain, alcian blue, and mucicarmine. Microscopic calcifications are usually found; foci of hyalinization, and bone formation.
Soft tissue tumors may also be present (Fig. 22-17). Mast cells are a typical feature, usually being more numerous in the spindle cell component.

Monophasic synovial sarcomas are as frequently diagnosed as the classic biphasic variety. These tumors are characterized by a monotonous, small spindle cell population lacking the gland-forming components typically seen in classic synovial sarcoma (Fig. 22-18). In these cases, positive identification depends on the demonstration of epithelial antigens by immunohistochemistry. Usually, only a few cells are positive for cytokeratin but rarely it may be the majority (Fig. 22-19).

Consistent specific translocation t(X:18)(p11.2;q11.2) is found in 90% of synovial sarcomas. This results in fusion of the SYT gene on chromosome 18 to the SSX1 or SSX2 gene on the X chromosome.

Synovial sarcoma has a high rate of local recurrence, as well as metastasis (Fig. 22-20). Although there is no consistent prognostic difference between biphasic and monophasic subtypes, patients whose tumors show SYT-SSX2 fusion are thought to have a better prognosis than those with SYT-SSX1 fusion.
Fibrosarcoma

Fibrosarcoma is a malignant tumor of fibroblasts, that is, collagen-producing cells, which show no other evidence of differentiation.

At one time, this was the most commonly diagnosed malignant connective tissue tumor. However, with the increasing use of immunohistochemistry, the segregation of desmoid tumors, monophasic synovial sarcoma, and benign reactive processes such as fasciitis, the diagnosis of fibrosarcoma has become a diagnosis of exclusion and is much less commonly made.

Most patients are in the 30s to 50s, and most of the tumors are seen on the extremities, more frequently the lower extremity. Generally, these individuals have slowly growing tumors, and in most cases, the tumor has been present 2 years or more when seen clinically. The tumor generally arises in the deep structures, either intramuscularly or in the intermuscular septae. Grossly the excised tumors are firm and gray-white in color (Fig. 22-21) and measure less than 10 cm in diameter.

**Fibrosarcoma**

*FIGURE 22-17* Photomicrograph to demonstrate a focus of calcification within a synovial sarcoma. (Calcification is more usual at the margins of the tumor [H&E, × 10 obj.].)

*FIGURE 22-18* A, Photomicrograph of a monophasic synovial sarcoma. Cytokeratin stains in such a case will show occasional positive epithelioid cells. Note the foci of hyalinized intercellular matrix, which is occasionally present (H&E, × 4 obj.). B, A cytokeratin stain (CAM 5.2) showed small islands of epithelioid cells (immunoperoxidase, × 10 obj.).

*FIGURE 22-19* A, The photomicrograph is of tissue removed from the elbow joint of a 27-year-old male who presented clinically with pain and limitation of motion. The clinical diagnosis was loose bodies and synovitis. The microscopic finding was of a spindle-cell neoplasm (B), which stained diffusely positive with vimentin antibody and focally positive with cytokeratin antibody (AE-1/AE-3). (Malignant synovial sarcoma is only very rarely seen in a joint.) ([A] H&E, × 4 obj.; [B] immunoperoxidase, × 4 obj.).
Microscopically, the lesions consist of uniform spindle cells with scanty cytoplasm that are organized into rather uniform fascicles. Mitoses are generally present but vary in number. Occasionally myxoid changes are seen in the matrix. The lesions are generally regarded as either well or poorly differentiated. In a well-differentiated fibrosarcoma, there is generally a very distinct herring-bone pattern with a variable degree of collagenization (Fig. 22-22). In the less well-differentiated tumors, there is generally more cellular crowding, more mitoses, a less distinct pattern, and foci of necrosis. With wide marginal excision, the 5-year survival rate for well-differentiated tumors is about 60%, whereas for poorly differentiated tumors, it is about 30%. Differentiation from monophasic synovial sarcoma or peripheral nerve sheath tumors requires immunohistochemical stains for accuracy. Many fibrosarcomas show limited evidence of muscle differentiation by immunohistochemistry, and these tumors are considered to be myofibrosarcomas (Fig. 22-23).

Two important variants of fibrosarcoma with confusingly similar names have been recognized in recent years. The more common type is designated myxofibrosarcoma and tends to occur in the subcutaneous tissue of the extremities in older adults in whom its insidiously infiltrative pattern of invasion along connective tissue and fascial planes makes excision with negative margins very difficult. Histology shows highly myxoid nodules within which large spindle cells with frank atypia tend to condense around curvilinear blood vessels (Fig. 22-24). High- and low-grade examples are recognized, with the former showing increased cellularity, mitotic activity, and (in about 30% of cases) metastasis.

Considerably less common is a low-grade fibromyxoid sarcoma (Evans tumor). This tumor also occurs preferentially in soft tissue of the extremities but generally affects younger adults than myxofibrosarcoma. Histology is deceptively innocuous, with monotonous spindle cells focally growing in biphasic collagenous and myxoid patterns (Fig. 22-25), which may mimic a variety of benign tumors (such as desmoid or neurofibroma). Recently, 7;16 and 11;16 translocations involving the FUS gene on chromosome 16 have been found in this tumor.

Ossifying Fibromyxoid Tumor of Soft Tissue

Ossifying fibromyxoid tumor of soft tissue is a rare neoplasm most often seen in the extremities of adults, although it may also occur in the trunk or head and neck region. Most often, it is subcutaneous but may occasionally occur in deeper tissue.
On imaging studies, they often have a calcified periphery, which on histologic examination is frequently osseous.

Most tumors are 4 to 6 cm in diameter and are made up of variable amounts of collagenized fibrous tissue and loose myxoid tissue, which may contain epithelioid cells. Cellularity is variable, and mitoses are rare. Thin-walled blood vessels are normally prominent (Fig. 22-26). Some cases may show increased cellularity, and more than two mitoses per 50 high power fields. Some of these cases may recur, and metastases have been reported. S100 protein is usually demonstrable.

**Malignant Peripheral Nerve Sheath Tumors (Malignant Neurilemoma)**

A malignant peripheral nerve sheath tumor (MPNST) is a spindle cell sarcoma that arises from a nerve or from a neurofibroma, or has histologic immunohistochemical or ultrastructural features believed to be characteristic of a nerve sheath. This tumor accounts for less than 10% of all soft tissue sarcomas, and up to half the cases occur in association with type I neurofibromatosis.
FIGURE 22-24 Myxofibrosarcoma showing large, atypical cells growing in myxoid matrix with associated curvilinear blood vessels (H&E, × 10 obj.). (Courtesy of Dr. Mark Edgar.)

FIGURE 22-25 Low-grade fibromyxoid sarcoma (Evans tumor) showing bland spindle cells in alternating pink collagenous and pale blue myxoid zones (H&E, × 10 obj.). (Courtesy of Dr. Mark Edgar.)

FIGURE 22-26 A, Lateral radiograph shows a large ossifying mass related to the proximal femoral diaphysis. B, Anteroposterior radiograph shows that the lesion is mostly medial. C, MRI shows a very large soft-tissue mass in this obese female. D, Lower power photomicrograph to show an area of bland bone formation in a cellular spindle cell tumor (H&E, × 4 obj.).
In patients with neurofibromatosis, the development of a painful mass should alert the clinician to the possibility of an MPNST. Most patients with MPNSTs are between the ages of 25 and 40 at the time of presentation.

Most cases are seen in relationship to major nerves of either the brachial or sciatic plexus and, hence, in the proximal upper or lower extremity.

Microscopically, most MPNSTs resemble fibrosarcomas in their pattern. However, unlike the symmetrical nuclei of fibroblasts, the nuclei in cases of MPNST are often wavy in outline; there may be nuclei palisading, and the lesion may demonstrate a nodular or plexiform arrangement (Fig. 22-27). Occasional cases of MPNST demonstrate myoblastic differentiation (Triton tumor), whereas others show vascular or epithelial differentiation. Mature islands of cartilage or bone may be present.

**FIGURE 22-26—CONT’D**

**E,** Higher power photomicrograph shows moderate collagen formation with a loose fibromyxoid stroma (H&E, × 10 obj.). **F,** High-power photomicrograph shows regular fibromyxoid cells with a pink lacy cytoplasm (H&E, × 25 obj.). (Courtesy of Dr. Michael Klein.)

**FIGURE 22-27**

A, Photomicrograph of a malignant peripheral nerve sheath tumor. At low power, there is a cellular spindle-cell lesion with a non-descript but focally nodular pattern (H&E, × 4 obj.). **B,** At a higher power, there are distinct foci of nuclear palisading in this field (H&E, × 10 obj.). **C,** Another field stained for S100 protein (× 10 obj.).
The microscopic differential diagnosis of MPNST from fibrosarcoma, monophasic synovial sarcoma, or leiomyosarcoma may be difficult. It depends on the morphology in addition to a careful evaluation of a panel of immunohistochemical stains. The most useful stain for nerve sheath differentiation is S100 protein. However, there are no specific markers and the careful evaluation of a panel of antigens is necessary to arriving at a correct diagnosis. It may be especially difficult to differentiate a cellular neurilemoma from an MPNST and impossible with a small biopsy. However, generally the S100 protein is more diffusely distributed in a neurilemoma and generally typical morphologic features of neurilemoma can be found: the Antoni A and B pattern. The rates of recurrence and metastases in MPNST are around 50%.

**Epithelioid Sarcoma**

Epithelioid sarcoma is a fully malignant, painless soft tissue sarcoma, which, when it first presents, is likely to be mistaken for granulation tissue, ulcerated squamous cell carcinoma, or a synovial sarcoma. The patients are generally young adults (aged 10 to 35), and men appear to be more frequently affected. These lesions most often present in the superficial subcutis or deep tendon sheaths of the hand, wrist, or fingers, but may also extend to involve the skin and ulcerate. The lesions vary considerably in size from a few millimeters in diameter to several centimeters. The smaller lesions in particular will tend to be underdiagnosed both clinically and pathologically. The histogenesis of this neoplasm remains obscure, but a synovial origin has been suggested.

On microscopic examination, epithelioid sarcoma is a nodular growth composed of a densely eosinophilic polyhedral cell population with prominent nucleoli and an epithelial appearance; however, occasionally the cells are spindled (Fig. 22-28). Pleomorphism is variable, and central necrosis may be evident. Immunohistochemical stains are generally positive with both vimentin and epithelial markers (Fig. 22-29). These tumors have a tendency to recur and may disseminate via the lymphatic and vascular systems, eventually leading to both lymph node and lung metastases. Although the long-term prognosis is poor, some patients may survive for many years with metastatic disease.

The treatment of choice is wide excision.

**Soft Tissue (Extraskeletal) Osteosarcoma**

Rare cases of bone-forming malignant mesenchymal tumors have been described in the soft tissues, usually intramuscularly and most commonly in the thigh. These are usually round to ovoid lesions.

![Figure 22-28](image)

**Figure 22-28**

A. In this patient with an epithelioid sarcoma, the tumor initially arose in the distal portion of the tendon sheath of the extensor pollicis longus. At amputation, as demonstrated in this photograph, the tumor was found to be in the subsynovial space, wrapping around the tendon.

B. Photomicrograph of an epithelioid sarcoma shows plump, oval to polyhedral cells that have a dense eosinophilic cytoplasm. The predominant pattern here is epithelial, but in other areas a spindle fibrosarcomatous appearance can be expected (H&E, × 10 obj.).

C. Higher power view of nests of epithelioid cells (H&E, × 40 obj.).
that exhibit radiographically trabeculated bone formation throughout. They occur in older individuals with a mean age of between 50 and 67 years. The duration of symptoms at the time of presentation is usually only a few months. In some cases, the lesion has been associated with prior radiotherapy.

Grossly, the excised tumors are soft to firm and gritty, and have a variegated hemorrhage and necrotic appearance. They may appear to be well circumscribed or infiltrative. Microscopically, they may be dense and fibroblastic or extremely cellular, with fine lace-like osteoid and mineralized bone (Fig. 22-30).

Because metaplastic bone is found in a variety of other mesenchymal tumors including synovial sarcoma, malignant fibrous histiocytoma, and liposarcoma, differential diagnosis may on occasion be very difficult. In general, the prognosis is poor with early metastases.

**Extraskelatal Myxoid Chondrosarcoma (Chordoid Tumor)**

Extraskelatal myxoid chondrosarcoma is a rare tumor that usually presents in the deep soft tissue of an extremity, most often the thigh or popliteal fossa. Generally, it is a slow-growing tumor and metastasizes late. Most of the patients are middle-aged or older, and men are more commonly affected.

Grossly, the tumor is generally well circumscribed with a soft to firm consistency. On sectioning, it characteristically has a nodular gelatinous appearance and there may be focal hemorrhage (Fig. 22-31A). From the gross appearance, the lesion is most likely to be initially diagnosed as a myxoid liposarcoma.

Microscopically, the cells are monomorphic and have small hyperchromatic nuclei with a thin rim of eosinophilic cytoplasm.

**FIGURE 22-29** A, Photomicrograph of an epithelioid sarcoma in the region of the hypothenar eminence that presented as a small, irritated nodule. There is a nodular pattern of swollen cells with smaller spindle cells running between them. In the lower right it is invading fat (H&E, ×10 obj). B, In another area of the tumor there are admixed chronic inflammatory cells (H&E, ×10 obj). It is perhaps not difficult to see that such an appearance may be confused with reparative tissue. C, Nearly all the cells stain for vimentin (immunoperoxidase, ×10 obj). D, The larger swollen cells, but not the smaller spindle cells, also stain for cytokeratin (CAM 5.2) (immunoperoxidase, ×10 obj).
FIGURE 22-30  

A, Radiograph of a 50-year-old man who presented with a small, painful mass in the calf region. A well-defined ossified lesion is evident in the soft tissue.  

B, Gross lesion resected from the patient in A.  

C, Radiograph of the specimen shows the formation of mineralized tissue throughout the lesion. There is no evidence of maturation of the bone toward the periphery, a finding in contrast to that found in myositis ossificans, a lesion that can be mistaken for a soft-tissue osteosarcoma.  

D, Photomicrograph to demonstrate malignant bone formation by a fibrous stroma (H&E, × 10 obj.).  

E, Higher power photomicrograph demonstrates a cellular stroma forming immature bone (H&E, × 25 obj.).
Frequently, the cells are arranged in short anastomosing strands with abundant extracellular mucoid matrix. Differentiated chondrocytes are rare in this tumor, which is now classified as a neoplasm of uncertain histogenesis. Mitotic figures are generally rare (Fig. 22-31B).

Immunohistochemical staining shows diffuse S100 staining in around 50% of cases; however, because most of the lesions in the differential diagnosis are S100 positive, this is not very helpful. Epithelial markers will be negative, which differentiates this lesion from chordoma and mixed tumors of salivary gland or sweat gland origin.

Extraskeletal myxoid chondrosarcoma is characterized by a balanced translocation t(9:22)(q22;q12) or t(9:17)(q22;q11).

Mesenchymal chondrosarcoma, which has already been discussed in Chapter 17, may also occur in the soft tissues in almost 25% of cases, mostly around the head and neck region or in the thigh.
FURTHER READING

GENERAL

Bones and Joints

Orthopedics and Rheumatology


Tumors
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SECTION I NORMAL

1. NORMAL SKELETAL STRUCTURE AND DEVELOPMENT

Matrix
Bones
Joints
Bone Growth and Development
\section{SECTION II: RESPONSE TO INJURY}
\section{4. THE EFFECTS OF INJURY AND THE INFLAMMATORY RESPONSE}
Effects of Injury
\section{The Inflammatory Response}
Vortkamp A: The Indian hedgehog-PTHrP system in bone development.


5. BONE AND JOINT INFECTION

Pyogenic Infections and Other Nongranulomatous Inflammatory Conditions


Granulomatous Inflammation of Bones and Joints


SECTION III: METABOLIC DISTURBANCES

6. DISEASES RESULTING FROM SYNTHESIS OF ABNORMAL MATRIX COMPONENTS

Disturbances in Collagen Synthesis


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FURTHER READING

554

7. DISEASES RESULTING FROM DISTURBANCES IN CELL LINKAGE

Osteosclerotic Conditions


8. BONE DISEASE RESULTING FROM DISTURBANCES IN MINERAL HOMEOSTASIS

Calcium and Phosphorus Homeostasis

Hypercalcemia

Hypocalcemia

SoFT Tissue Calcification

9. ACCUMULATION OF ABNORMAL METABOLIC PRODUCTS AND VARIOUS HEMATOLOGIC DISORDERS

Deposition and Storage Disease

FURTHER READING 555
Skeletal Manifestations of Hematologic Diseases

SECTION IV: ARTHRITIS
10. THE DYSFUNCTIONAL JOINT

Function and Anatomy

Normal Joint Physiology

The Pathophysiology of a Dysfunctional Joint

11. THE NONINFLAMMATORY ARTHRITIDES
Osteoarthritis (Degenerative Joint Disease)
Ochronosis

Arthritis Secondary to Subchondral Insufficiency Fracture

Rapidly Destructive Osteoarthritis

Osteochondritis Dissecans

Diseases Resulting from the Deposition of Metabolic Products in the Joint Tissues

Inflammatory Arthritis Associated with Diffuse Connective Tissue Disease

Degenerative Arthritis

Ankylosing Spondyloarthropathies
14. TISSUE RESPONSE TO AND COMPLICATIONS OF ORTHOPAEDIC IMPLANTS

Usual Tissue Response to Clinically Nonfailed Articular Implants


Morbidity Associated with Total Joint Replacements


Tissues Responses Around Noninfected, Clinically Failed Articular Implants


15. BONE INFARCTION (OSTEONECROSIS)

Skeletal Manifestation of Decompression Sickness (Caisson Disease)


Bone Infarction Not Associated with Caisson Disease


Osteonecrosis of the Femoral Head


Staging of Osteonecrosis of the Femoral Head


Legg-Calvé-Perthes Disease


Idiopathic, Nontraumatic or Primary Osteonecrosis of the Femoral Head


SECTION V: BONE TUMORS

16. BONE-FORMING TUMORS AND TUMOR-LIKE CONDITIONS

Reactive or Post-Traumatic Lesions that May Be Mistaken for Malignant Tumors


Benign Tumors

Malignant Tumors

17. CARTILAGE-FORMING TUMORS AND TUMOR-LIKE CONDITIONS

Benign Tumors


**Benign Neoplasms**


**Malignant Neoplasms**


**18. FIBROUS TUMORS AND TUMOR-LIKE CONDITIONS**

**Reactive or Post-Traumatic Tumors**


**Benign Neoplasms**


Malignant Neoplasms


19. BENIGN NONMATRIX-PRODUCING BONE TUMORS

Reactive or Post-Traumatic Tumors


Benign Tumors Including Neoplasms


20. MALIGNANT NONMATRIX-PRODUCING BONE TUMORS

Ewing's Sarcoma


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Immunohematopoietic Neoplasms


Vascular Neoplasms


Metastatic Cancer


21. BENIGN SOFT TISSUE TUMORS

Benign Synovial Lesions


Benign Fibrous Lesions


Peripheral Nerve Lesions


Miscellaneous Lesions


22. MALIGNANT SOFT TISSUE TUMORS

Malignant Fibrous Histiocytoma


Liposarcoma


Rhabdomyosarcoma


Synovial Sarcoma


Fibrosarcoma


Ossifying Fibromyxoid Tumor of Soft Tissue

Malignant Peripheral Nerve Sheath Tumors (Malignant Neurilemoma)

Epithelioid Sarcoma

Soft Tissue (Extraskeletal) Osteosarcoma

Extraskeletal Myxoid Chondrosarcoma (Chordoid Tumor)
Index

Note: Page numbers followed by f refer to figures; page numbers followed by t refer to tables; page numbers followed by b refer to boxes.

A
Abnormal trabecular pattern, 64–65, 65f focal, 65, 66f
generalized, 64–65, 65f, 66f
Abscess. See also Infection; Osteomyelitis Brodie’s, 125, 126f
femoral, 126f
femoral neck, 126f
lung, 85f
tuberculous, 128
vertebral, 120
Achilles tendon
rupture of, 94
xanthoma of, 218–219, 219f
Achondroplasia, 158, 159f, 160f
Acid-fast bacilli, 129–130, 132
Acid phosphatase
in inflammation, 88–90
in juvenile Paget’s disease, 171–172
Acid phosphatase stain, 47
Acquired immunodeficiency syndrome (AIDS), 119, 127
Acromelic dwarfism, 159
Acromial bursa, calcifications of, 210f
Actin, 47
in myofibrosarcoma, 543f
Actinomycoses israeli infection, 114, 114f, 115f
Acute inflammatory reaction, 88–90
Acute rheumatoid disease, 280. See also Rheumatoid arthritis
Adamantinoma
differentiated, 438–441, 441f, 442f long bone, 446, 447f, 448f osteolobus dysplasia and, 441
Adenocarcinoma, 492, 493f
Adenoma, parathyroid, 192–193, 195f. See also Hyperparathyroidism
Adolescent coxa vara, 274–275, 274f, 275f
Age
tagrarcen decrease with, 4–5
aneurysmal bone cyst and, 453–454, 456f bone loss with, 175–177. See also Osteoporosis bone tumor distribution by, 66–67, 67f chondroblastoma and, 410–412, 412f chondromyxoid fibroma and, 413–414, 414f chordoma and, 425, 425f enchondroma and, 405, 408f eosiophilic granuloma and, 462, 463f
Ewing’s sarcoma and, 478, 478f
femoral head changes and, 22f
fibrosarcoma and, 443, 443f
fibrous dysplasia and, 435f

giant cell tumor and, 466–471, 471f hydroxypatite changes with, 4
intervertebral disc changes with, 304, 304f
Intramedullary chondrosarcoma and, 417, 417f
joint changes with, 21, 22f, 236
lymphoma and, 481, 481f
meniscal changes with, 22f, 105–106, 107f nonossifying fibroma and, 430f
osteoblastoma and, 374, 376f osteochondroma and, 400, 400f
osteoid osteoma and, 370, 371f osteosarcoma and, 380–381, 380f, 383, 391f
unicamer al bone cyst and, 453, 453f
f Osteoarthritis; Rheumatoid See also Osteoarthritis; Rheumatoid arthritis
Aorta, in Marfan’s syndrome, 151, 153f Arteriole, inflammation of, in rheumatoid arthritis, 285f Arthritis, 232. See also Osteoarthritis; Rheumatoid arthritis; Septic arthritis chondromalacia in, 239, 241f cracking in, 239, 239f degenerative, 310–314 eburnation in, 238f, 239f erosion in, 239, 240f extrinsic repair in, 241–242, 243f, 245f fibillation in, 238f, 239 fibracartilagineous tissue in, 242–244, 244f ghosting in, 239–241, 241f inflammatory, 280–289. See also Rheumatoid arthritis metabolic product deposition and, 289–301. See also specific crystal deposition diseases synovial fluid examination in. See Synovial fluid, examination of transient, 119 intrinsic repair in, 241, 242f, 245f joint shape in, 236, 238f ligamentous injury in, 248–249 loose bodies in, 245–248, 246f, 247f, 248f, 249f metalloproteinases in, 244 necrosis in, 239–241, 241f, 242f noninflammatory, 254. See also Osteoarthritis pathophysiology of, 235–251, 238f psoriatic, 289, 292f subarticular cysts in, 245, 246f subchondral bone injury in, 244–245, 245f suppurrative, 119 synovial fluid examination in, 251, 251f, 251t, 252t synovial membrane injury in, 249–251, 249f, 250f, 251f
in synphils, 120 tissue alterations in, 236–238 types of, 235–236
Bone tumor (Continued)
calciﬁcation (Continued)
calcium (Continued)
Calcium (Continued)
Calcium (Continued)
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Calcium (Continued)
Calcium (Continued)
Calcium (Continued)
Calcium (Continued)
Calcium (Continued)
Chondrocyte(s) (Continued)
metabolic functions of, 233, 234f
necrotic, 84–85, 86f, 239–241, 241f, 242f
in ochronosis, 267f
in Ollier's disease, 405, 406f
in osteoarthritides, 259f, 260–261, 260f
in osteochondroma, 403f, 404f
reparative, 103, 105f
stress effects on, 235, 238f
Chondroitin sulfate, 4f, 46f
Chondrolipoma, 521, 522f
Chondrolysis, in slipped capital femoral epiphysis, 274–275
Chondroma.
See also Chondroitin sulfate, 4, 6f
Clinical presentation, 70–74
Claudication, pseudoneurogenic, 312
Claudications, 275–276
Clavicle
Clavicle fracture, 103f
Coccyst (Continued)
cortex, chondroma of, 426f
cromdor's triangle, 69, 69f, 381–382, 382f
COL, 294
collagen, 2–3, 3f
antibodies against, 48, 50f
in desmoplastic fibroma, 441–443, 443f
fiber-forming, 4
hyalinization of, 87–88, 87f
meniscal, 104–105
organ distribution of, 5f
in pigmented villonodular synovitis, 504–505, 507f
staining of, 45–47, 48f
structure of, 2–3, 3f
synthesis of, 3–4, 4f
disorders of, 142–152, 142f
See also Ehlers-Danlos syndrome; Marfan's syndrome;
Osteogenesis imperfecta; Scurvy
S-100 positivity in, 423
radiography of, 423f
in synovial sarcoma, 539
in Ollier's disease, 405, 406f
family history in, 69f
age and, 413–414, 414f
radiography in, 67, 67f
specimen radiography in, 46f
radiography of, 71, 72f
fibular, 46f
intramedullary, 417–420
age and, 417f, 417f
dedifferentiation of, 419–420, 421f
dig of, 418–419, 421f
evendrroma, 418–419
grade I, 417f, 420f
grade II, 417f, 418f, 418f, 420f
grade III, 418f
imaging of, 417f, 418f
location of, 417f, 417f, 418f
metastasis with, 419f
mesenchymal, 420–421, 422f, 549f
malignant, 457–549, 549f
radiography of, 71f, 72f
vs. Schmorl's node, 308–310
vs. soft-tissue chondroma, 526–529
specimen radiography in, 46f
Chordae tendineae, in Hurler's syndrome, 154f
Chordoid tumor, 547f–549, 549f
Chordoma, 425–426, 427f
age and, 425, 425f
chondroid, 426, 428f
imaging of, 425, 426f
location of, 425, 425f
vs. notochordal rest, 426, 428f
Chromosomes, 48
abnormalities of, 48
translocation of, 48
Chronic nets, 114–115, 115f
Chronic recurrent multifocal osteomyelitis, 115–116, 116f
Cladication, pseudo-(neurogenic), 312d
Clavicle
chronic recurrent multifocal osteomyelitis of, 115–116, 116f
congenital pseudoarthrosis of, 105f
formation of, 32
in hyperparathyroidism, 196f
osteomyelitis of, 112f
Clear cell chondrosarcoma, 421–425
giant cells in, 424f, 425
radiography of, 423f, 424–425, 424f
S-100 positivity in, 423f, 425
Clinical presentation, 70–74
Clivus, chordoma of, 428f
CML, 7f
Coccidioidomycosis, 133–134, 136f
Coccyst, chondroma of, 426f
cromdor's triangle, 69, 69f, 381–382, 382f
COL, 294
collagen, 2–3, 3f
antibodies against, 48, 50f
in desmoplastic fibroma, 441–443, 443f
fiber-forming, 4
hyalinization of, 87–88, 87f
meniscal, 104–105
organ distribution of, 5f
in pigmented villonodular synovitis, 504–505, 507f
staining of, 45–47, 48f
structure of, 2–3, 3f
synthesis of, 3–4, 4f
disorders of, 142–152, 142f
See also Ehlers-Danlos syndrome; Marfan's syndrome;
Osteogenesis imperfecta; Scurvy
S-100 positivity in, 423
radiography of, 423f
in synovial sarcoma, 539
in Ollier's disease, 405, 406f
family history in, 69f
age and, 413–414, 414f
radiography in, 67, 67f
specimen radiography in, 46f
radiography of, 71, 72f
fibular, 46f
intramedullary, 417–420
age and, 417f, 417f
dedifferentiation of, 419–420, 421f
dig of, 418–419, 421f
evendrroma, 418–419
grade I, 417f, 420f
grade II, 417f, 418f, 418f, 420f
grade III, 418f
imaging of, 417f, 418f
location of, 417f, 417f, 418f
metastasis with, 419f
mesenchymal, 420–421, 422f, 549f
malignant, 457–549, 549f
radiography of, 71f, 72f
vs. Schmorl's node, 308–310
vs. soft-tissue chondroma, 526–529
specimen radiography in, 46f
Chordae tendineae, in Hurler's syndrome, 154f
Chordoid tumor, 547f–549, 549f
Chordoma, 425–426, 427f
age and, 425, 425f
chondroid, 426, 428f
imaging of, 425, 426f
location of, 425, 425f
vs. notochordal rest, 426, 428f
Chromosomes, 48
abnormalities of, 48
translocation of, 48
Chronic nets, 114–115, 115f
Chronic recurrent multifocal osteomyelitis, 115–116, 116f
Cladication, pseudo-(neurogenic), 312d
Clavicle
chronic recurrent multifocal osteomyelitis of, 115–116, 116f
congenital pseudoarthrosis of, 105f
formation of, 32
in hyperparathyroidism, 196f
osteomyelitis of, 112f
Clear cell chondrosarcoma, 421–425
giant cells in, 424f, 425
radiography of, 423f, 424–425, 424f
S-100 positivity in, 423f, 425
Clinical presentation, 70–74
Clivus, chordoma of, 428f
CML, 7f
Coccidioidomycosis, 133–134, 136f
Coxa vara, 274–275, 274f, 275f
CPPD. See Calcium pyrophosphate dihydrate deposition disease (CPPD)
Cracking, of articular cartilage, 239, 239f
Cranial nerves, 21, 23f
Cranium. See also Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
Cranial sutures, 21, 22
570 iNDEX
Femoral head (Continued)
rheumatoid arthritis of, 282f
screw track in, 323f
specimen radiography of, 44f
subchondral fracture of, 266–269, 267f, 268f, 269f
Femoral neck
abscess of, 126f
exostoses of, 403f
fracture of, 181f, 347–348, 350f
synovial sarcoma of, 539f, 540f
Femur. See also Femoral head
abscess of, 126f
amyloidosis of, 215f
aneurysmal bone cyst of, 457f
benign fibrous histiocytoma of, 434f
blood supply to, 2–3
bony spur of, 97–98
calcification in, 209f
Camurati-Engelmann disease of, 174–175, 179f
Chester-Erdheim disease of, 467f
chondrosarcoma of, 407f, 420f, 421f, 422f
in congenital syphilis, 121f
desmoid tumor of, 430f
diaphysis of, 7f, 10f
echinococcal cyst of, 138f, 139f
in Ehlers-Danlos syndrome, 150f
enchondroma of, 409f
eosinophilic granuloma of, 464f
epiphysis of, 2–3, 10f
fetal, 30f, 32f, 33f
fibromyxoma of, 416f
fibrosarcoma of, 444f
fibrous dysplasia of, 435f, 440f
Gaucher’s disease of, 216–218, 217f
giant cell tumor of, 471f
Gorham’s massive osteolysis of, 186f
growth plate of, 10f, 37f
in juvenile Paget’s disease, 177f
juxtacortical chondroma of, 411f
linear calcification in, 346f
lipid granulomatosis of, 467f
loading conditions of, 9f
malignant fibrous histiocytoma of, 68f, 445f
metaphysis of, 2–3, 10f
in Morquio’s disease, 155f
myelomeningocele-related fracture in, 94, 97f
myofibrosarcoma of, 543f
nonossifying fibroma of, 431f, 432f
ossifying fibromyxoid tumor of, 544f
osteoblastoma of, 379f
osteochondroma of, 401f
osteogenesis imperfecta of, 146f, 148f
osteoid osteoma of, 372f
osteomyelitis, 120f
osteomyelitis of, 112f, 125f
osteopathia striata of, 368f
osteopetrosis of, 164f
osteoporosis of, 181f
osteosarcoma of, 69f, 75f, 381f, 382f, 383f, 385f, 386f,
389f, 392f, 395f
Paget’s disease of, 62f, 65f, 168, 171f, 173f, 177f
periosteal desmoid tumor of, 430
polyostotic fibrous dysplasia of, 440f
pseudotumor of, 301f
rickets of, 204f
in scurvy, 151f, 152f
secondary center of ossification of, 34f
septic arthritis of, 119f
shepherd’s crook deformity of, 434–435, 435f
in sickle cell disease, 225f
spindle-cell sarcoma of, 421f
synovial chondromatosis of, 501f
trabeculae of, 7f, 9f
transient osteoporosis of, 185f
tumor vs. marrow of, 70f
unicameral cyst of, 455f
in vitamin A intoxication, 200f
Fibers of Sharpey. See Sharpey’s fibers
Fibrillation, of articular cartilage, 238f, 239, 240f
Fibrillin-1, 151
Fibrinous loose (rice) bodies, 248, 285f
Fibro-osseous dysplasia/lesion. See Fibrous dysplasia
Fibroblast, 6–7, 91, 91f
Fibroblast growth factors, 16t

Fibrocartilage, 26–27
reparative, 241–244, 243f, 244f
Fibrocartilaginous mesenchymoma, 439f
Fibrocartilaginous metaplasia, 26–27, 28f
Fibrodysplasia (myositis) ossificans progressiva,
525–526, 527f
Fibrolipomatous hamartoma, 521
Fibroma
calcifying aponeurotic, 514–515, 514f
chondromyxoid, 413–416, 415f
age and, 413–414, 414f
imaging of, 414, 415f
location of, 413–414, 414f
desmoplastic, 441–443, 442f, 443f
nonossifying. See Nonossifying fibroma
ossifying (osteofibrous dysplasia), 438–441, 441f,
442f
adamantioma and, 441
tendon sheath, 507, 509f, 510f
Fibromatosis, 507–515
aggressive, 508–511, 511f, 512f
aponeurotic, juvenile, 514–515, 514f
extra-abdominal, 508–511, 511f, 512f
palmar, 511–514, 513f, 514f
plantar, 514
Fibromodulin, 5, 7f
Fibromyxoid sarcoma, low-grade, 542, 544f
Fibromyxoma, 416–417, 416f
Fibronectin, 5–6, 7f
Fibrosarcoma, 443–444, 444f, 445f
age and, 443, 443f
differential diagnosis of, 444
herringbone pattern in, 444, 444f,
542, 542f
imaging of, 443–444, 444f
location of, 443, 443f
soft tissue, 541–542, 542f
Fibrosis
in melorheostosis, 366
peritrabecular, 194, 197f
Fibrous cortical defect. See Nonossifying fibroma
Fibrous dysplasia, 432–438
age and, 435f
aneurysmal bone cyst and, 455, 458f
bone spicules in, 436, 438f
cartilaginous areas in, 436, 439f
cementicle-like structure in, 436, 439f
craniofacial, 432–434, 435f
cystic changes in, 436, 438f
fracture in, 434–435, 435f, 436, 439f
ground-glass appearance in, 435, 436f, 437f
imaging of, 435, 436f, 437f
location of, 432–434, 435f
osteoclastic resorption in, 436, 439f
vs. osteofibrous dysplasia, 441
polyostotic, 69–70, 436–438, 440f
radiography in, 69, 72f
of rib, 435–436, 437f
sarcomatous transformation in, 436
shepherd’s crook deformity in, 434–435, 435f
specimen radiography in, 437f
storiform pattern in, 436, 439f
Fibrous histiocytoma
benign, 430f, 431–432, 434f. See also Nonossifying
fibroma
malignant, 444–446
radiography in, 68f, 444–445, 445f
soft-tissue, 534–535, 534f
storiform pattern in, 445–446, 446f,
534, 534f
Fibrous tumor. See also specific tumors
bone
benign, 432–443
malignant, 443–446
reactive/post-traumatic, 430–432
soft tissue
benign, 506–518
malignant, 534–535
Fibroxanthoma, 431–432, 434f
Fibula
adamantinoma of, 446
chondromyxoid fibroma of, 415f
chondrosarcoma of, 46f
congenital pseudoarthrosis of, 104f

Fibula (Continued)
enchondroma of, 409f
Ewing’s sarcoma of, 479f
lipoma of, 475f
membranous lipodystrophy of, 220f
nonossifying fibroma of, 433f
osteochondroma of, 72f
osteofibrous dysplasia of, 438–441
osteogenesis imperfecta of, 145f, 147f
Paget’s disease of, 167f
unicameral bone cyst in, 455f
Finger. See also Phalanges
trigger, 95–96, 96f
FISH, 48–49
Fixation, tissue, 43–44, 45
Flame edge, in Paget’s disease, 62f
Flexion contracture, 93f
Florid reactive periostitis, 362, 362f
Fluorapatite, 157
Fluorescence in-situ hybridization (FISH), 48–49
Fluorescence labeling, 50–52, 51f
Fluorescent stain, 48
Fluoride
normal levels of, 157–158
in osteoporosis, 158–159, 158f, 159f
Fluorosis, 61, 157–158, 158f, 159f
Foot
bone islands in, 368f
calcifying aponeurotic fibroma of, 514f
giantism of, 523f
gout of, 78f
hallux rigidus of, 257f
hallux valgus of, 255–257, 257f
infarction in, 344f
lipoma of, 476f
melorheostosis of, 368f
membranous lipodystrophy of, 220f
Morton’s neuroma of, 519–520, 519f, 520f
osteoblastoma of, 379f
osteoid osteoma of, 373f
osteomalacia of, 201f
osteomyelitis of, 115f
phleboliths in, 525f
plantar fibromatosis of, 514
reflex sympathetic atrophy of, 64f
transient osteoporosis of, 184f
Forearm. See Radius. Ulna
Foreign body reaction, 322, 324, 325f
to Collagraft, 322f
to Gortex fibers, 322f
implant-related, 334, 338f
Forestier’s disease. See Ankylosing hyperostosis
Formalin, 44
Fracture(s), 96–98
avulsion, 97–98, 98f, 99f
banana, 163f
cement lines in, 98, 99f
comminuted, 99
complications of, 102
compound, 99
compressive, 98, 100f
differential diagnosis of, 99–100, 103f
echinococcal cyst and, 139f
in elderly patients, 96, 96f
fat embolization with, 102, 104f
femoral condyle, 55f
femoral neck, 181f, 347–348, 350f
in fibrous dysplasia, 434–435, 435f, 436, 439f
helical, 98, 100f
in hemangiopericytoma, 491f
hemorrhage with, 99, 101f, 102f
humeral, 482f, 491f
meningomyelocele-related, 96, 97f
metatarsal, 201f
micro-, 97, 97f
multiple, 102
necrosis with, 99, 101f, 102f
in non-Hodgkin’s lymphoma, 482f
nonaccidental, 96
nonunion of, 99, 101f, 113f
oblique, 98, 100f
odontoid, 144
in osteogenesis imperfecta, 143, 143f, 144, 145f,
146f, 147, 147f, 147t


Hip (Continued)
  in Morquio's disease, 155f
  myositis ossificans progressiva of, 527f
  normal, 240
  osteoarthritis of, 256f, 257f, 259f, 262–263, 263f,
  264f, 271f
  osteomyelitis of, 120f
  osteosarcoma of, 330f, 354, 356f
  oxalosis of, 211f
  Paget's disease of, 167f
  pigmented villonodular synovitis of, 502–504, 503f
  prosthetic. See Orthopaedic implants rapidly destructive osteoarthritis of, 271f
  saddle deformity of, 276f
  septic arthritis of, 119f, 280f
  slipped capital femoral epiphyses of, 274–275, 274f,
  275f
  synovial chondromatosis of, 500, 500f, 501f
  transient osteoporosis of, 64, 185f
  tuberculosis of, 128f
  Histamine, 88
  Histiocytes, 89f
  in atypical mycobacterial infection, 131f
  in bone infarction, 344f
  of brown tumor, 198f
  in calcific tendinitis, 209f
  in Chester-Edreheim disease, 463, 467f
  in eosinophilic granuloma, 462–463, 465f
  Gaucher's, 218, 218f
  in gout, 293f
  in Hodgkin's disease, 483f
  implant-related, 325f, 331f, 332f, 333f, 335f, 337f
  metal-filled, 325f
  in oxalosis, 213f
  in pigmented villonodular synovitis, 506f
  in rapidly destructive osteoarthritis, 270–273, 272f
  in Rosai-Dorfman disease, 464, 468f
  in sarcoidosis, 133f, 135f
  in tuberculosis, 130f
  in xanthoma, 219f
  Histiocytoma
  fibrous
  benign, 430f, 431–432, 434f. See also Nonossifying fibroma
  malignant, 444–446
  radiography in, 68f, 444–445, 445f
  soft-tissue, 534–535, 534f
  storiform pattern in, 445–446, 446f, 534f, 534f
  synovial, benign. See Pigmented villonodular synovitis
  Histocompatibility antigen
  DR4, 281
  DW4, 281
  HLA-B27, 315–317
  Hodgkin's lymphoma, 483, 483f
  Hoffa's disease, 498, 499f
  Homocystinuria, 151
  Homogentisic acid, 265, 265f
  Hormones, in calcium homeostasis, 190–192, 191f,
  192f, 193f
  Hounsfield units, 36, 56f
  Howship's lacunae, 12–15, 14f
  HPRTI, 293
  Humeral head
  calcification in, 346f
  osteonecrosis of, 349f
  Humerus (Continued)
  Rosai-Dorfman disease of, 468f
  in sickle cell disease, 126f
  tuberculosis of, 129f
  unicameral bone cyst in, 454f
  Humoral hypercalcemia, 198–200
  Hunter, John, 2f
  Hunter, William, 232–233
  Hunter syndrome, 154
  Hurley-Scheie syndrome, 154
  Hurley's syndrome, 154f, 154f, 155–156, 155f
  Hyaline cartilage. See Articular cartilage
  Hyaluronan, 4, 6f, 7f
  Hyaluronidase deficiency, 154f
  Hydatid cyst, 134, 138f, 139f
  Hydroxyapatite, 4
  age-related effects on, 4
  in fluorosis, 157
  in osteochondrosis, 310, 310f
  periosteal, 9–10
  soft tissue, 293–294, 295f
  stain for, 45–47, 49f
  trauma-related deposition of, 207, 209f, 210f
  in tumoral calcinosis, 208–210
  Hydroxyproline, 15–16
  urinary, 167, 171–172
  Hypercalcemia, 192–200
  cancer-related, 198–200
  clinical features of, 194f
  differential diagnosis of, 194b
  humoral, 198–200
  Hypercalcemic crisis, 193
  Hypercalciumia, in Paget's disease, 167
  Hyperlipidemia, primary, 218–220, 219f
  Hyperosteoidosis, 190f, 200–201, 200f, 201f
  Hypertension
  angiotensin. See Angiotensin hyperostosis
  cranial, 432–434, 435f
  infantile cortical, 117–118, 118f
  in melorheostosis, 364–366, 367f
  hyperparathyroidism, in, 190, 192–198, 194f, 195f
  brown tumor of, 198f, 199f
  dissecting resorption in, 190f, 194–198, 197f,
  198f
  erosive resorption in, 194, 196f, 197f
  increased skeletal density in, 198, 199f
  osteocytic osteolysis in, 194–198
  vs. Paget's disease, 168–170
  peritrabecular fibrosis in, 194, 195f
  primary, 192–193, 194f, 195f
  radiography in, 194, 196f
  of hand, 196f
  of skull, 197f
  of tooth, 196f
  salt and pepper appearance in, 194, 197f
  secondary, 190, 193–194, 198, 199f
  specimen radiography in, 196f, 197f
  treatment of, 193, 194
  Hyperphosphatasia
  vs. Paget's disease, 173
  primary (juvenile Paget's disease), 171–173
  Hyperphosphatemia, in tumoral calcinosis, 207–208, 208f
  Hypersensitivity, methylmethacrylate-related, 331
  Hypertrophic pulmonary osteoarthropathy, 311–312
  Hypertrichosis, 116–117, 117f
  Hypertricosis, 290
  clinical stages of, 291
  crystal deposition in, 291, 294f
  radiography in, 293f
  secondary, 290–291
  Hypervitaminosis A, 200, 200f
  Hypocalcemia, 178, 200–205
  clinical features of, 206f
  Hypocalcemia, 200–205, 204f
  familial, 205, 205f
  mesenchymal tumor and, 204–205, 204f
  tumoral calcinosis and, 207–208
  Hypotension, methylmethacrylate-related, 331
Metabolic disease. See also specific diseases and bone disorders
cell linkage disturbance–related, 162–187. See also Osteopenia; Osteoporosis; Osteosclerosis
collagen synthesis–related, 142–152
deposition/storage disturbance–related, 211–230
inborn error–related, 152–155
mineral formation disturbance–related, 156–158
mineral homeostasis disturbance–related, 189–210. See also Osteogenesis; Calcification; Hypercalcemia;
Hypocalcemia
Metacarpals
Camurati-Engelmann disease of, 179
fibrous dysplasia of, 436
fibrous dysplasia of, 436
fibrous dysplasia of, 436
fibrous dysplasia of, 436
fibrous dysplasia of, 436
focal sclerosis in, 62
vs. amyloidosis, 213
blood vessels of, 37
hypersensitivity reaction to, 331
fibrous capsule with, 324, 325
bone-implant interface with, 326–327, 327
fracture of, 201
fibromatosis of, 512
Giant cell tumor of, 472
fetal, 31
Calcification, soft tissue
stains for, 45–52
Microradiography, 547–549, 549
Osteopenia; Osteoporosis; Osteosclerosis
Monosodium urate crystals, 291, 292
Mononuclear cells, 88
Non-Hodgkin's lymphoma, 481–483, 482
Nonunited, 99, 101
Nonspecific urethritis, 119
Nodular tenosynovitis, 529–530
Nuclear factor kappa-B ligand, 15
Nucleus, 82
Osteosclerosis
Myelofibrosis, 61, 226–227, 228
Myelofibrosis
in arthritis, 239–241, 241f, 242
aseptic vs. septic, 346
avascular, of femoral head. See Femoral head, osteonecrosis of cuneiform, 87
in compartment syndrome, 92–94, 93f, 94f
fracture–related, 99, 102f, 267–268, 269
injury–related, 84–85, 84
marrow, 84–85, 85f, 344, 345
muscle, 92–94, 93f, 94f
in osteomyelitis, 122–125, 124
septic vs. aseptic, 346
Neisseria gonorrhoeae infection, 119–120
Neonatal osteomyelitis, 112–113, 112
Nerves
benign lesions of, 519–521
in Charcot's spine, 312–314
injury to, 94–96, 95f
Neurilemma
benign, 520, 521f
malignant, 543–545, 545f
Neuroblastoma
vs. Ewing's sarcoma, 480
Neurofibroma
malignant, 520, 521f
neurofibromatosis, 103
type 1, 520, 521, 521f, 543–545
Neurofilament protein, 47
Neurogenic claudication, 312
Neuroma
Morton's, 519–520, 519f, 520f
traumatic, 518–519, 519f
Neuropathic (Charcot's) spine, 312–314, 314
Neuropathy
diabetic, 79
median nerve, 95–96, 95f, 96f
Neurophysiology, 119–120, 121f, 312–314, 314
Neurotrophins, 88
NF2, 520
Nieman-Pick disease, 218
Nitric acid, for decalcification, 44, 47f
Nitric oxide, 86
Nitrogen, tissue accumulation of. See Depreciation sickness
Nodular fascitis, 515, 516f
Nodular tenosynovitis, 529–530
Node
in osteogenesis imperfecta, 147, 148f
in rheumatoid arthritis, 285, 289f, 290f
Non-Hodgkin's lymphoma, 481–483, 482f
Nonionizing radiation imaging techniques, 58–60. See also Magnetic resonance imaging (MRI);
Ultrasoundography
Nonmatrix-producing bone tumor. See also specific tumors
benign, 449–476
malignant, 47f–492
reactive/post-traumatic, 450–453
Nononsifying fibroma, 430–432, 430f, 433f
age and, 430f
imaging of, 68f, 430–431, 431f, 432f
location of, 430f
specimen radiography of, 433f
storiform pattern in, 431–432, 433f
Nonspecific urethritis, 119
Nonunion, 99, 101f, 113f
Nora's lesion (bizarre parosteal osteochondromatous proliferation), 363–364, 363f, 364f
Normarks opticis, 51–52, 51f
Notochordal rest, 426, 428
Nuclear factor kappa-B ligand, 15
Nucleus, 82f
pyknotic, 84, 84f
Nucleus pulposus, 20–21, 21f. See also Intervertebral disc
Nutrient arteries, 10, 11f
Osteogenic sarcoma. See Osteosarcoma

Osteogrophicia, 2, 2f

Osteoid, 12, 12f, 13f, 14f
aluminum-related, 194, 195f
in eosinophils, 159
increase in, 200–201, 200f, 201f
in osteomalacia, 201–202, 202f
in osteoporosis, 180–181, 183f
in osteosclerosis of obscure etiology, 179f
staining of, 49f
in vitamin D deficiency, 190f

Osteoid osteoma, 370–374
age and, 370, 371f
vs. Brodie’s abscess, 125
of femur, 372f
of finger, 372f
imaging of, 73f
location of, 370, 371f
nidor (lucent zone) of, 45f, 371f, 372f, 373, 373f, 374f
of os calcis, 373f
vs. osteoblastoma, 375
specimen radiography in, 42, 45f, 373, 375f
of spine, 371–373, 374f
synovitis with, 371–373
of toe, 371f

Osteoid osteosarcoma, 12f, 13f, 14f
in hyperosteoidosis, 200, 200f
in osteogenesis imperfecta, 148

Osteologia Nova, 2, 2f

Osteolysis
in adaminatoma, 446, 447f
idiopathic, 185–187
implant-associated, 113–114, 114f
massive (Gorham’s), 186–187, 186f
in mastocytosis, 469f
osteoctic, 194–198
in osteoibrous dysplasia, 440, 441f
in osteoporosis, 185f

Osteoma
calvarial, 368–370, 368f
colonic polyps and, 369–370
facial, 368–370, 370f
knee, 369f
osteoid. See Osteoid osteoma

Osteomalacia, 63, 63f, 200–202, 201b, 202f
aluminum-related, 194
in Fanconi’s syndrome, 205
in hypophosphatemia, 204–205
oncogenic, 204–205, 204f
radiography in, 63, 63f, 64f, 201, 201f

Osteomyelitis
Actinomyces israelii in, 114, 114f, 115f
amyloidosis and, 115
blood culture in, 114–115
bone culture in, 122, 124f
vs. bone tumor, 125f
of bowel, 75, 75f
chronic, 114–115, 115f
differential diagnosis of, 110, 110f, 112, 112f
fracture-related, 113, 113f
in Gaucher’s disease, 125–127, 218, 218f
hematogenous, 110–112
in adult, 110–112
in children, 110, 111f
differential diagnosis of, 112, 112f
in elderly individuals, 111–112, 112f
in intravenous drug users, 110–111, 111f, 123f
sites of, 110, 111f
historical perspective on, 110
iatrogenic, 113–114, 114f
imaging of, 120–122, 123f
inflammatory response in, 122–125, 124f, 126f
involucrum in, 125, 125f
joint spread of, 118, 118f
magnetic resonance imaging in, 120–121, 123f
morbid anatomy of, 122–127, 124f, 125f
multifocal, recurrent, chronic, 115–116, 116f
in necrosis in, 122–125, 124f
neonatal, 112–113, 112f
vs. osteoblastoma, 375
vs. osteoid osteoma, 371
in osteopetrosis, 126–127
polyostotic, 112–113, 112f
radiolucence scanning in, 57f, 121–122, 123f

Osteomyelitis (Continued)
Salmomelina in, 125–126, 127f
sequestrum in, 125, 125f
in sickle cell disease, 125–126, 126f, 225, 226f
spinal, 120–121
squamous cell carcinoma and, 115
surgery and, 113–114, 114f
vs. transient osteoporosis, 185
trauma-related, 113–114, 113f
Osteon, 17–18, 17f
bone volume in, 180–181, 183f
in osteoporosis, 180–181, 183
vs. osteonecrosis, 267–268, 267f
in pregnancy, 183, 185f
radiography in, 45f, 63, 63f
sclerodurancy of, 45f
in scurvy, 150
in sickle cell disease, 222–223
sodium fluoride in, 158, 158f
specimen radiography in, 45f
subchondral insufficiency fracture and, 266–268, 267f
in thalassemia, 227f
trabecluae in, 181, 184f
treatment of, 158, 159f, 182–183
type I (postmenopausal), 177, 178, 181f, 183f
hip fracture in, 267–268, 267f, 267f
type II (senile), 177, 178, 180–181, 181f, 183f
Osteoporosis circumscripta, 167–168, 169f
Osteoprotegerin, 190–191
Osteosarcoma (osteogenic sarcoma), 376–386
central, high-grade, 380–382
age and, 380–381, 380f
Codman’s triangle in, 381–382, 382f
location of, 380–381, 380f
lytic, 381–382, 381f
matrix in, 382, 383f, 384f
periosteal new bone formation in, 381–382, 381f
in Rothmund-Thompson syndrome, 382, 387f
sclerotic, 381–382, 381f
soft tissue expansion of, 381–382, 381f
sunburst appearance in, 381–382, 381f
telangiectatic, 382, 385f, 386f
central, low-grade, 382–383, 389f
sclerotic, 382–383, 388f
classification of, 376, 380f
definition of, 376, 380f
differential diagnosis of, 376–378, 380b
in dog, 329, 330f
high-grade, 378–380, 380f
of hip, 354, 356f
implant-related, 329
intracortical, 385, 396f
low-grade, 378–380, 380f
multifocal, 378
parosteal, low grade (juxtacortical), 383–385, 392f, 393f
age and, 383, 391f
genetics of, 385
imaging of, 383, 391f, 393f
location of, 383, 391f
treatment of, 385
periosteal, 385, 394f, 395f
radiography in, 69, 69f, 387f, 388f, 391f, 393f, 394f, 395f
soft-tissue (extraskeletal), 546–547, 548f
surface, high grade, 385
treatment of, 385–386
Osteosclerosis, 162–175.
Osteopetrosis;
Paget’s disease
Camurati-Engelmann, 173–175, 179f
medullary, monomelic, localized, 173, 178f
of obscure etiology, 175, 179f
Oxalosis, 212
crystals in, 212, 213f
primary, 212, 212f
radiography in, 212, 212f
secondary, 212

P

Paget’s disease, 165–173
alkaline phosphatase in, 167
arthritis in, 166, 167f
bowing in, 166, 167f
burnt out phase of, 170, 174f
Pelvis
amalyoidosis of, 215f
avulsion fracture of, 97–98, 98f
chondromyxoid fibroma of, 72f
chronic recurrent multifocal osteomyelitis of, 115–116, 116f
in congenital syphilis, 314f
in juvenile Paget's disease, 177f
osteoblastoma of, 377f
osteopetrosis of, 387f
osteoporosis of, 181f
osteosarcoma of, 389f
oxalosis of, 212f
Paget's disease of, 65f
sarcoidosis of, 135f
Periosteal chondroma, 408, 411f
Periosteal desmoid tumor, 430, 430f
Periosteal osteosarcoma, 385, 394f, 395f
Periosteum, 9–10, 10f, 11f
blood supply of, 10–11, 11f
cambium layer of, 10, 11f
embryonic, 30–32, 31f
fibrous layer of, 10, 11f
post-traumatic reaction in, 9–10, 10f
Periostitis
reactive, florid, 362, 362f
syphilis-related, 121f
Peripheral nerves
benign lesions of, 519–521
injury to, 94–96, 95f
Periarterial fibrosis, 194, 197f
Periostitis, 88–90
PET. See Positron emission tomography (PET)
Phagocyte, 88–90, 89f
Phalanges
bizarre, sarcoideal osteochondromatous proliferation of, 363f, 364f
chondroma of, 451f, 529f
enchondroma of, 408f
epidermoid inclusion cyst of, 450, 450f
Exophiala jeaneselmei infection of, 134, 137f
fibrous dysplasia of, 436f
giant cell tumor of, 530f
glomus tumor of, 451f
gout of, 78f
hemangiomatosis/lymphangiomatosis of, 461f
Hodgkin's lymphoma of, 482f
in hyperparathyroidism, 196f
in hypertrophic pulmonary osteoarthropathy, 117f
juxta cortical chondroma of, 411f
lymphoma of, 482f
metastatic disease of, 495f
osteoaclasis of, 387f
ostioide osteoma of, 371f, 373f
osteomyelitis of, 126f
osteosarcoma of, 387f
pigmented villonodular synovitis of, 502f
reactive periostitis of, 362f
sarcoidosis of, 132–133, 134f
in sickle cell disease, 66f, 224f
Phlebitis, in hemangioma, 523–524, 525f
Phosphohexosamninuric, 156–157, 156f, 157f, 158f
Phosphorus. See also Hyperphosphatemia;
Hyperphosphatemia: Hypophosphatemia
Phosphorylase
homeostasis of, 190–192, 191f, 192f
Photography, 42–43, 46f
Physiologic horizons, 42f
Physio. See Growth plate
Picture-frame appearance, 168, 170f, 171f
Pigmen, giant in, 293f
Pigmented villonodular synovitis (PVNS), 501–506, 506f
collagen in, 504–505, 507f
differential diagnosis of, 505, 508f
genetics of, 505–506
giant cells in, 504–505, 506f
vs. hemophilia, 300–301
vs. hemosiderotic synovitis, 108, 108f, 485, 486f
imaging of, 502f, 503f, 504f
of knee, 504, 505f
pseudosarcomatous appearance in, 504–505, 507f
specimen radiography in, 503f
synovial membrane in, 250–251, 251f
Plantar fibromatosis, 514
Plasma cell(s), 90, 90f
in esoinophilic granuloma, 462–463, 465f
in multiple myeloma, 485, 487f
in rheumatoid arthritis, 283f, 508f
in Rosai-Dorfman disease, 468f
Plassmacytoma, 485, 488f, 489f
Platelet-derived growth factor, 16f
Pleomorphic hyalinizing angiectatic tumor, 506, 509f
Pleomorphic liposarcoma, 623, 535f, 536f
PMMA. See Polymethylmethacrylate (PMMA)
POEMS syndrome, 485
Polarized light microscopy, 45–47, 51–52, 51f
in amyloidosis, 214, 216f
for synovial fluid examination, 298–299, 299f, 300f
Polyethylene implant, 323–324
astroid bodies with, 334, 337f
carbon filaments with, 334, 339f
debris deposition with, 331, 331f, 333f
failure of, 334, 334f, 337f, 337f, 339f
femoral head migration into, 331f
synovial reaction with, 334f
Polymethylmethacrylate (PMMA), 323–324, 323f,
334–335, 339f, 340f
barium sulfate with, 323–324, 324f, 328–329,
334–335, 340f
bone-cement interface with, 326, 326f
of failed implant, 332, 333f
foamy histiocytes with, 334–335, 340f
in frozen-tissue section, 334–335, 339f
hypertension with, 331
improper implanting of, 329, 329f
mante of, 326, 326f
necrotic rim with, 326
in paraffin section, 334–335, 340f
tissue effects of, 324, 326f, 326f
two-phase nature of, 324f
zirconium with, 335, 340f
Polymorphonuclear leukocytes, 88–90, 89f
in joint infection, 280, 280f
in osteomyelitis, 124f
in rheumatoid arthritis, 281f, 284f
in septic arthritis, 119, 120f, 280f
Polyostotic fibrous dysplasia, 69–70, 436–438, 440f
Polyostotic osteomyelitis, 112–113, 112f
Polyps, colonic, 369–370
Popliteal cyst, 282, 287f, 292f
Positron emission tomography (PET), 57–58
in lymphoma, 58f
in osteoblastoma, 379f
Post-traumatic tumors. See also specific tumors
bone-forming, 362–364
fibrous, 435–432
nonmatrix-producing, 450–453
Posterior longitudinal ligament, ossification of, 317, 318f
Pott's disease, 127–128
Pregnancy, osteosarcoma in, 183, 185f
Primary hyperparathyroidism, 218–220, 219f
Primitive bone. See Woven bone
Primitive neuroectodermal tumor. See Ewing's sarcoma
Programmed cell death, 85–86, 86f
Progressive diaphysal dysplasia, 173–175, 179f
Prolapse, intervertebral disc, 305, 305f
Prostate cancer
metastatic, 495f
osteomalacia with, 204–205
Prosthetic implant. See Orthopaedic implants
Proteoglycans, 4, 5f
antibodies against, 48
diminished staining of, 235, 237f, 241f
metalloproteinase breakdown of, 244
staining of, 25–26, 25f, 48f, 48f, 241f
synthesis of, 6f, zonal distribution of, 25–26, 25f
Proteus syndrome, 521
Pseudo-(neurogenic) claudication, 312
Pseudoarthrosis, congenital, 102–103, 104f, 105f
Pseudogout, 78f, 299f
See also Calcium pyrophosphate deposition disease
Pseudohypoparathyroidism, 198–200
Pseudohypothyroidism, 202–203
Soft tissue tumor, 497–532
benign. See also specific tumors
cartilaginous, 526–529
fatty, 521–522
fibrous, 506–518
giant cell, 529–530, 530f
peripheral nerve, 518–521
syndial, 498–506
vascular, 522–525
imaging strategies in, 75–78, 76f, 77f
malignant, 534–549. See also specific tumors
bone-forming, 546–547
epithelialid, 546
fibroblast, 541–542
fibromyxoid, 542–543
fibrous, 535–537
muscle, 537–539
nerve sheath, 543–546
syndial, 539–541
Solid aneurysmal bone cyst. See Giant cell reparative granuloma
Solitary bone cyst. See Bone cyst, unicameral
Solitary enostosis, 364, 365f
Solitary (localized) myeloma, 485, 488f, 489f
Solitary neurofibroma, 520–521f, 521f
Specimen examination. See Examination methods; Gross examination; Microscopic examination
Specimen fixation, 43–44, 45
Specimen photography, 42f, 43f, 46f
Spinal cord(s)
in Chester-Erdheim disease, 467f
in epithelialid sarcoma, 547f
in malignant fibrous histiocytoma, 534f
in metastatic cancer, 493f, 494f
in myelofibroma, 516f
in myofibrosarcoma, 543f
in myositis ossificans circumscripta, 528f
in neurofibromatosis, 521f
in pleomorphic hyalinizing angiectatic tumor, 509f
Spindle-cell sarcoma
in chondrosarcoma, 419–420, 421f
in Paget's disease, 170, 175f
Spine (vertebrae). See also Intervertebral disc
aneurysmal bone cyst of, 454, 457f
ankylosing hyperostosis of, 317, 317f, 318f
hip replacement and, 317, 319f
posterior longitudinal ligament ossification with, 317, 318f
ankylosing spondylitis of, 315–317, 316f
bipola, 316f
chondromyxoid fibroma of, 415f
chondrosarcoma of, 71f, 418f
chorda of, 425–426, 426f, 427f
codfish, 181f
degenerative spondylolisthesis of, 311, 313f
in Ehlers-Danlos syndrome, 150, 151f
eosinophilic granuloma of, 462, 464f
facet joint load in, 311
fish-mouth, 178, 182f
fluoride effects on, 158, 158f
ganglion cyst of, 530, 532f
Gaucher's disease of, 216–218, 217f
hemangiomia of, 46f, 460f, 462f
hereditary osteomylits of, 110–111, 111f
Hodgkin's disease of, 483f
in Hurler's syndrome, 155–156, 155f
in hyperparathyroidism, 196f, 197f
infection of, 120
in intravenous drug user, 110–111, 111f
inflammatory spondylitis of, 315
inflammatory spondyloarthropathy of, 315
juvenile kyphosis of, 311, 311f, 312f
leukemia of, 44f, 485f
in Marfan's syndrome, 153f
metastatic cancer of, 496f
in Morquio's syndrome, 154f, 155f
multiple myeloma of, 486f
myotic infection of, 133–134, 136f
myelofibrosis of, 228f
myositis ossificans progressiva of, 527f
neuropathic (Charcot's), 312–314, 314f
Stress fracture, 63, 64f, 97f, 98f, 201
vs. osteoid ostema, 371
stress risers, 353
Stromelysins, 244
Subarticular cyst, 245, 246f
Subchondral bone
arthritis-related injury to, 244–245, 245f, 282–285, 288f
fracture of, 96, 96f
femoral condyle, 268–269, 270f
femoral head, 266–269, 267f, 268f, 269f, 270–273, 271f, 277f
Subungual exostosis, 362–363, 363f
Sudek's atrophy, 183, 184f
Sulfur granules, eosinophilic, 115f
Sunlight exposure, 191, 193f
Suppurative arthritis, 119
Surgery, osteomyelitis and, 113–114, 114f
Suture, giant cell reaction with, 91, 92f
Swelling, in inflammation, 88
Symphysis (amphiarthrodial joint), 19–20, 20f, 21f
Symphysis pubis, in hyperparathyroidism, 196f,
Syntophysin, 48
Synarthrosis, 21, 22f
Syndesmophytes, 317, 318f
Synovial chondromatosis, 498–501, 500f, 501f, 502f
Synovial effusion
in prosthetic implant evaluation, 333, 335f
in rheumatoid arthritis, 281, 281f
Synovial fluid, examination of
in arthritis, 251, 251f, 252f
in CPPD, 298–299, 299f
in gout, 298
in rheumatoid arthritis, 281, 281f
in hemangioma, 498, 498f, 499f
Synovial histiocytoma, benign. See Pigmented villonodular synovitis
Synovial lining cells, 27–29, 28f
type A, 29, 29f
type B, 29, 29f, 30f
Synovial membrane, 27–29, 28f, 29f
amyloidosis of, 216f
arthritis-related injury to, 249–251, 249f, 250f, 251f
in Charcot's joint, 255f
fibrous exude of, 285f
frozen section of, 52f
functions of, 29
in hemophilia, 250–251, 251f
hemosiderin deposition in, 106–108, 108f, 223f,
30f, 29f, 508f
hyperplasia of, 84, 84f, 87f, 106–108, 108f,
in hemophilia, 300–301, 301f
in osteoarthritis, 249, 249f, 250–251, 250f
in rheumatoid arthritis, 281–282, 282f, 283f
hypertrophy of, 249f, 250f, 250–251, 281–282, 288f
injury to, 106–108, 108f, 249–251, 249f, 250f, 251f
macl cells of, 283f
ochronosis of, 267f
in osteoarthritis, 255f, 261f, 262f
in pigmented villonodular synovitis, 250–251, 251f
in rapidly destructive osteoarthrits, 273, 273f
in rheumatoid arthritis, 281–282, 283f, 284f
type A cells of, 29, 29f
type B cells of, 29, 29f, 30f
villous lipomatous proliferation of, 498, 499f,
Synovial sarcoma, 539–541, 540f
biphase, 539, 540f
calcification in, 539–540, 541f
vs. fibrosarcoma, 444
imaging of, 539, 539f, 540f
metastatic, 540–541, 547f
monophase, 539, 540, 541f
positive identification of, 540, 541f
recurrence of, 540–541
Synoviocytes, 27–29
proliferation of, 84, 84f
Synovitis
crystal, 52, 291, 298–299, 299f, 300f
hemosiderotic, 106–108, 108f, 505, 508f
inflammatory. See Rheumatoid arthritis
osteoid osteoma and, 371–373
traumatic, 106–108, 108f
villonodular, pigmented. See Pigmented villonodular synovitis
Woven bone (Continued)
in myelofibrosis, 228f/
in osteoarthritis, 257–260, 259f/
in osteoblastoma, 378f/
in osteoid osteoma, 372f, 375f/
Wrist
amyloidosis of, 216f/
Chester-Erdheim disease of, 466f/
clear-cell chondrosarcoma of, 423f/

Wrist (Continued)
Kienböck’s disease of, 346–347, 347f/
lipid granulomatosis of, 466f/
membranous lipodystrophy of, 220f/
pigmented villonodular synovitis of, 502–504, 504f/
rheumatoid arthritis of, 280f/
rickets of, 63f/
ultrasonography of, 59f/

X
X-ray. See Radiography
Xanthomatosis, 218–220, 219f/

Z
Zirconium, 335, 340f/