To the list of orthopaedic osteonecrotic syndromes, one may add the list of transient ischemia phenomena that may explain bizarre puzzling spectra of illnesses, including transient osteoporosis, Sudeck atrophy, and reflex sympathetic dystrophy (RSD) syndrome (5).

In considering osteonecrosis, arterial disruption is the most explicable pathogenesis, the most common example being that of osteonecrosis following femoral neck fractures. Elegant studies by Crock (6) and others have clearly demonstrated the fine but tenuous arterial supplies to the femoral head (Fig. 14.1). Although there is some arterial supply from vessels from the ligamentum teres, the medial circumflex branch of the femoral artery supplies most of the femoral head. This arterial vasculature courses along the femoral neck and is quite susceptible to disruption with subcapital fractures of the neck, particularly displaced subcapital fractures of the neck. The blood supply to the femoral head is primarily from the medial circumflex artery, with its deep branch the most important. The deep branch terminates as the posterior superior nutrient arteries that enter the head of the femur via the vascular foramina in the posterior-superior and anterior-superior quadrants of the femoral head and neck (7). The incidence of osteonecrosis following displaced femoral neck fractures has been reported to be as high as 84 percent in the literature. Given the tenuousness of the circulation, it is remarkable that not all femoral neck fractures eventuate in bone necrosis.

A contributing factor to osteonecrosis following hip fracture may be a tamponade effect caused by hemarthrosis-induced increased intracapsular pressure.

Pathologically, the events following arterial disruption have been clearly described (8,9). The classic features of osteonecrosis are characterized by loss of cells—hematopoietic, fatty, and bone cells (Table 14.1). Although risk factors and clinical associations have been identified, the pathogenesis of osteonecrosis is still unknown (1). Theories such as fat emboli, fatty induced intraosseous pressure, intravascular coagulation, microfractures, apoptosis of osteoblasts and osteocytes, and others continue to be explored.

Coagulation disorders such as seen in thrombophilia (increased predisposition to clots) and hypofibrinolysis (decreased ability to lyse clots) have been increasingly associated with osteonecrosis.

Mankin (2) has classified osteonecrosis as the result of mechanical vascular interruption, thrombosis, and embolism, injury to or pressure on a vessel wall, or that due to venous occlusion (Table 14.1). The most common cause of osteonecrosis is that which follows trauma, especially the osteonecrosis that follows femoral neck fractures in the elderly. Fractures at this site are thought to compromise an already tenuous blood supply, the deep branch of the medial circumflex artery (3). Osteonecrosis is known to complicate developmental problems such as slipped capital femoral epiphysis and the femoral head deformities seen in Legg-Calvé-Perthes disease in childhood. Osteochondritis dissecans is a well-described osteonecrotic entity, most commonly seen in the medial aspect of the lateral femoral condyle. Numerous anatomically consistent sites exist where osteonecrosis may be observed either idiopathically or following trauma (Table 14.2).

Hall (4) has articulated the preference of these osteonecrotic syndromes for convex as opposed to concave subarticular areas of the bone. He attributed the predilection for these sites to the larger cartilaginous (and thus avascular) covering of convex subarticular surfaces, which may result in a more tenuous blood supply or more concentrated biomechanical forces transmitted across this type of surface. Although trauma is generally thought to be the etiology in these syndromes, the etiology in males, in weight-bearing areas, and particularly in some clinical syndromes related to stress, such as the capitellum in adolescent baseball pitchers or tennis players, suggests a multifactorial etiology (4).
cortical bone (9). In ischemic necrosis, initially fat necrosis and death of hematopoietic cells are noted, followed in several weeks by loss of osteocytes. Characteristically, the bone looks acellular, with empty ghostlike osteocytic lacunae and no evidence of osteoblast surface activity (Fig. 14.2). Osteonecrotic tissue often shows evidence of past remodeling such as creeping substitution or juxtaposition of new bone, suggesting that following the initial ischemia the bone-forming potential is stimulated. Most probably, the length of the ischemic episode dictates the extent to which, if possible, remodeling and new formation can occur. Obviously, terminal ischemia, that is, complete disruption of the only arterial supply, results in irreversible death. It has been estimated that, with ischemia, in less than 2 hours the changes that occur in osteocytes are probably reversible, but most likely irreversible damage occurs after 4 hours (10). Correlation with light microscopic features has been made (Table 14.3).

Changes thought to be reversible are electron microscopically detectable condensation of nuclear chromatin and irregularities of the cytoskeleton. Irreversible changes seen later include coarse aggregation of chromatin, broadening of the interchromatin

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mechanism*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic osteonecrosis (fracture)</td>
<td>MVI, VVO</td>
</tr>
<tr>
<td>Septic osteonecrosis</td>
<td>MVI, T&amp;E,</td>
</tr>
<tr>
<td>Nontraumatic osteonecrosis (adults)</td>
<td>I/P-VW, VVO(?)</td>
</tr>
<tr>
<td>Stress or fatigue fractures</td>
<td>MVI, VVO</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>T&amp;E, I/P-VW, VVO(?)</td>
</tr>
<tr>
<td>Dysbarism (caisson’s disease, decompression</td>
<td>T&amp;E, I/P-VW</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>I/P-VW</td>
</tr>
<tr>
<td>Connective-tissue disorders (e.g., rheumatoid</td>
<td>MVI, I/P-VW</td>
</tr>
<tr>
<td>Arteritis or vasculitis</td>
<td>I/P-VW</td>
</tr>
<tr>
<td>Hemoglobinopathy (sickle cell disease)</td>
<td>T&amp;E</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>T&amp;E, I/P-VW</td>
</tr>
<tr>
<td>Radiation injury</td>
<td>I/P-VW</td>
</tr>
<tr>
<td>Corticosteroid administration</td>
<td>MVI, T&amp;E, I/P-VW, VVO(?)</td>
</tr>
<tr>
<td>“Aging”-related lesions of the distal femur</td>
<td>I/P-VW</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>VVO(?)</td>
</tr>
<tr>
<td>Gout</td>
<td>Secondary event</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>?</td>
</tr>
<tr>
<td>&quot;Idiopathic&quot; or spontaneous osteonecrosis</td>
<td>?</td>
</tr>
<tr>
<td>Childhood diseases (e.g., Legg-Calvé-Perthes,</td>
<td>?</td>
</tr>
<tr>
<td>Sever, Kohler, Larsen, Blount, or Panner disease)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders (polycythemia)</td>
<td></td>
</tr>
<tr>
<td>Fat emboli</td>
<td></td>
</tr>
</tbody>
</table>

*Putative pathogenetic mechanism: MVI, mechanical vascular interruption; VVO, venous and venular occlusion (Chandler disease); T&E, thrombosis and embolism; I/P-VW, injury to or external pressure on vessel wall.

bone ischemia, James and Steijn-Myagkaya (11) showed irreversible damage at 24 hours and empty lacunae after 24 hours. Despite the slow loss of osteocytic nuclei, traditionally a hallmark of osteonecrosis, the bone is most likely dead after the vascular injury and long before all cellular detail is lost. Therefore, the pathologist interpreting histopathologic sections, relying solely on cellular criteria of osteocytic empty lacuna spaces, may underdiagnose the presence of osteonecrosis.

To summarize, the changes seen histopathologically in bone undergoing necrosis are sequential and affect hematopoietic cells, marrow fat, and bone cells in a chronological fashion. Hematopoietic cells are the first to undergo anoxic death in approximately 6 to 12 hours. This is followed by the death of bone cells (osteocytes, osteoclasts, and osteoblasts) in 12 to 48 hours and subsequently marrow fat in 48 hours to 5 days.

Variability in the sensitivity of the various bone cells and marrow cells to anoxia raises the intriguing question of when the necrosis of one element is irreversible in leading to necrosis of the entire tissue. Intuitively, some reversibility is possible, perhaps explaining the enigmatic entities of reflex sympathetic dystrophy, bone bruise, bone marrow edema syndrome, and transient osteoporosis, the etiologies of which may, in part, be due to transient ischemia or anoxia rather than irreversible full necrosis.

The identification of dead bone is initially best assessed by necrosis of hematopoietic cells and fat cells. Although the loss of nuclei in lacuna spaces may be seen within a few days, it is usually not complete until several weeks and, in the nontraumatized sections of bone adjacent to fracture, may not be evident for several more weeks. In addition, empty bone lacunae may be a technical artifact due to inadequate dehydration or fixation or decalcification. The reparative response is characterized by a fibrovascular proliferation, including macrophages, and the subsequent juxtaposition of new bone on top of necrotic cancellous bone by active osteoblast proliferation. Concomitant areas of active osteoclastic resorption of dead bone may also be obvious.

### TABLE 14.2 Clinicopathologic Sites and Syndromes Associated with Osteonecrosis

| 1. Posttraumatic—femoral neck fractures, proximal half of scapoid, posterior half of talus |
| 2. Avascular necrosis of the hip—(N.B., convex surfaces) knee, talus (especially after dislocation), carpal (especially after dislocation), other: humerus, tibia, radius |
| 3. Slipped capital femoral epiphysis |
| 4. Legg–Calvé–Perthes disease (femoral head osteonecrosis) |
| 5. Osteochondritis dissecans (knee) |
| 6. ? Reflex sympathetic dystrophy |
| 7. Freiberg disease (osteonecrosis of the distal metatarsal bone) |
| 8. Kienbock disease (osteonecrosis of the carpal lunate) |
| 9. Kohler disease (osteonecrosis of the tarsal navicular) |
| 10. Panner disease (osteonecrosis of the capitellum) |
| 11. Other: talar dome, femoral condyle, humeral head |

---

![Figure 14.1](image1)

**FIGURE 14.1.** Vascularity of the femoral head. Specimen radiograph (A) and gross femoral head (Continued)
TABLE 14.3 Timetable of Microscopic Bone Changes in Osteonecrosis

<table>
<thead>
<tr>
<th>Time</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 h</td>
<td>Irreversible damage rabbit model (10,11)</td>
</tr>
<tr>
<td>&lt;6 h</td>
<td>Loss of osteocyte nuclear DNA; irreversible cell damage</td>
</tr>
<tr>
<td>&gt;6 h</td>
<td>Histologic deterioration of bone marrow cells and osteoblasts</td>
</tr>
<tr>
<td>24</td>
<td>Pyknosis of osteocyte nuclei; initial losses noted</td>
</tr>
<tr>
<td>2nd d</td>
<td>Ghostlike foggy appearance of marrow</td>
</tr>
<tr>
<td>3 d</td>
<td>Decreased affinity of osteocyte nuclei for H&amp;E and Feulgen stains</td>
</tr>
<tr>
<td>2–4 wk</td>
<td>Definitive loss of osteocytes in light microscopic sections (9)</td>
</tr>
</tbody>
</table>

h = hours, d = days, wk = weeks
H&E, hematoxylin and eosin.

FIGURE 14.1. (Continued) (B) (A, medial femoral artery; B, cervical arteries; C, subcapital zone; D, site of subcapital fracture) and (C) (A, cervical arteries; B, site of subcapital fractures; C, lateral circulation) with arterial injection showing fine tenuous arterial circulation to the femoral head, a site at great risk for disruption at the time of subcapital fractures (D). (After Crock HV. A revision of the anatomy of the arteries supplying the upper end of the human femur. J Anat. 1965;99:77–88.)

Generally, necrotic bone is identified histologically by poorly staining cortical and trabecular bone with the loss of nuclear detail as mentioned previously. The marrow itself usually undergoes change, which may be identified in early reversible stages as replacement by foamy macrophages (lipophages). A fuzzy disruption of the normal distinct clear fatty lobules is often evident as well as the appearance of small degenerating fat cells. Saponification of fat in necrotic marrow is identified as fine granular and flocculent, faintly eosinophilic, or deeply staining granules. More obvious calcification similar to that seen in dystrophic calcification states is eventually noted. Calcification of marrow is the end stage of marrow necrosis, the result of free fatty acids from dead marrow fat cells reacting with available released calcium. These calcifying sites lie dormant and usually are nonprogressive. Often asymptomatic, they appear only clinically as a clue that previous infarction has occurred.

Bone necrosis confined to the medullary cavity is often irreversible. However, osteonecrosis involving both cortical and cancellous bone appears more resilient in its reparative potential (2). Postinjury hyperemia gives way to a vascular fibrous repair revascularizing the dead bone. Both osteoclastic resorption of dead bone and osteoblast production of new bone ensue often juxtaposed on previous necrotic spicules.

Clinically, osteonecrosis is usually associated with pain.
FIGURE 14.2. Dead bone. Dead bone has a gross (A) and microscopic pallor (B) (lack of staining intensity). The bone characteristically lacks nuclei in osteocyte lacunar spaces (B, C) and, until phagocytic activity ensues, also lacks surface remodeling by osteoblasts and osteoclasts. The marrow simultaneously undergoes necrosis with loss of nuclei of fat or marrow cells, and a foggy appearance ensues followed by fibrosis of marrow (D) or even saponification (calcification of the fat) (E). Attempts at repair include new bone apposition. This creeping substitution may be jagged (F) or smooth (Continued)
Eventually, the bone is resorbed with large osteoclast-type resorption spaces (H). Thrombi may be observed in osteonecrosis, giving credibility to thrombophilia as a significant etiologic event (I). In some cases, ischemic marrow and microfractures support a link between subchondral insufficiency fractures and osteonecrosis (J). Infarcted bone and fat may be associated with a bluish discoloration of the mineralized tissue (K, L).

**FIGURE 14.2. (Continued)** (G). Eventually, the bone is resorbed with large osteoclast-type resorption spaces (H). Thrombi may be observed in osteonecrosis, giving credibility to thrombophilia as a significant etiologic event (I). In some cases, ischemic marrow and microfractures support a link between subchondral insufficiency fractures and osteonecrosis (J). Infarcted bone and fat may be associated with a bluish discoloration of the mineralized tissue (K, L).
Roentgenographically, osteonecrosis may be identified by a decreased uptake on bone scan in its early phase. Several weeks later, intense uptake can be noted owing to several factors: the hyperemia of the reparative response and mineralization of new bone to replace old bone. When saponification of dead marrow fat occurs, x-ray densities can be noted (12) (Fig. 14.3). Magnetic resonance imaging (MRI) classically shows a reduced signal in both T1- and T2-weighted images. Hypervascular reparative tissue may vary signal intensity (2).

Practical applications of MRI in the imaging of osteonecrosis of the femoral head include detection of early or small lesions, to differentiation of osteonecrosis from other processes, and to

FIGURE 14.3. Roentgenographic, bone scan, and magnetic resonance imaging (MRI) findings in osteonecrosis. Fuzzy, irregular radiopacities are typical of late-stage osteonecrosis on routine x-rays, distal femoral condyle (A). Bone scan is hot, due to both hypervascularity and new bone production in hip (B). (C–F) Areas of necrosis in the medial femoral condyle as demonstrated on MRI images; all images are fast-spin echo. C and D are proton density (TR 4,000; TE 30/EF). (Continued)
Involvement is common, as is bilaterality. Knee, shoulder, and ankle joints are also commonly involved. A large group of clinical syndromes associated with osteonecrosis have been documented (Table 14.2). Idiopathic (“avascular” or “aseptic”) osteonecrosis of the femoral head is the most completely studied.

Multifocal osteonecrosis, defined as disease involving three or more anatomical sites, is most often associated with corticosteroid therapy, especially in the treatment of lupus. Femoral head involvement is common, as is bilaterality. Knee, shoulder, and ankle joints are also commonly involved.

A large group of clinical syndromes associated with osteonecrosis have been documented (Table 14.2). Idiopathic (“avascular” or “aseptic”) osteonecrosis of the femoral head is the most completely studied.

**Idiopathic Necrosis**

Avascular necrosis of the bone is a significant cause of arthritis of the hip (12), the knee (14, 15), and other major joints (Table 14.4).

**TABLE 14.4 Causes of Osteonecrosis of the Femoral Head in One Large Series**

<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>No. of Resected Femoral Heads</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteonecrosis, all cases</td>
<td>345</td>
<td>337</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postfracture osteonecrosis</td>
<td>113</td>
<td>112 (mean age 49 y)</td>
<td>120 (mean age 55 y)</td>
<td>113</td>
</tr>
<tr>
<td>Idiopathic osteonecrosis, all cases</td>
<td>232</td>
<td>112 (mean age 49 y)</td>
<td>120 (mean age 55 y)</td>
<td>264</td>
</tr>
<tr>
<td>Idiopathic osteonecrosis, excluding lesions developing in osteoarthritis or rheumatoid arthritis</td>
<td>187</td>
<td>95 (mean age 46 y)</td>
<td>92 (mean age 53 y)</td>
<td>211</td>
</tr>
<tr>
<td>Idiopathic osteonecrosis, developing in osteoarthritis</td>
<td>37</td>
<td>15 (mean age 67 y)</td>
<td>22 (mean age 66 y)</td>
<td>40</td>
</tr>
<tr>
<td>Idiopathic osteonecrosis, developing in rheumatoid arthritis</td>
<td>8</td>
<td>1 (age 44 y)</td>
<td>7 (mean age 54 y)</td>
<td>13</td>
</tr>
</tbody>
</table>

Spontaneous Osteonecrosis of the Knee

A link between osteonecrosis and (insufficiency) fractures has been proposed in the condition referred to as spontaneous osteonecrosis of the knee (SPONK or SONK). These patients, usually elderly, develop pain predilected to the medial femoral condyle. Histopathologic findings consistent with fracture remodeling have led to the suggestion that the primary event leading to SPONK is a subchondral insufficiency fracture and that localized osteonecrosis seen in association with the disorder is the result of a fracture (14). Distinctions between SPONK and secondary causes of osteonecrosis of the knee have been drawn (15). Unlike the osteonecrosis secondarily associated with corticosteroids, ischemia, or atraumatic necrosis, SPONK is typically noted in older patients with no known risk factors and is usually unilateral with one condyle involved. Other joint involvement is rare. SPONK is located usually in a subchondral or epiphyseal region. In secondary osteonecrosis, patients are typically younger (>55 years) with bilateral disease often involving multiple condyles and multiple joints. Lesions may be diaphyseal, metaphyseal, or epiphyseal (15).

Avascular/Aseptic Necrosis

In the femoral head, avascular necrosis (AVN) has been estimated to develop in 10,000 to 20,000 new patients per year in the United States, and accounts for 5 to 12 percent of total hip replacements (1). It is termed avascular because there is no definitively identified vascular disruption, and aseptic because it is not related to infection.

AVN of the femoral head is more common in males, and its peak incidence is in the fourth decade. Conservative treatment options appear to delay but not halt the progression of the disorder (16).

Areas of osteonecrosis that are immediately adjacent to an articular joint may result in arthritis owing to a fracture of the necrotic bone and subsequent collapse of the overlying articular surface (Fig. 14.4).

The clinical onset of avascular AVN is usually sudden, although local pain may be present from months to years. Furthermore, the duration of symptoms is shorter than that in either rheumatoid arthritis or osteoarthritis. The hip seems to be the joint most commonly affected by an infarct. It occurs in the femoral head rather than the acetabulum. In this regard, it is generally true that the convex surface of any joint is most often affected. Avascular necrosis of the femoral head occurs in the subchondral bone of the superolateral or weight-bearing area of the femoral head. It may involve more than one skeletal site. Multiple lesions are often symmetrical, often varying in clinicopathologic significance.

The characteristic radiologic features of AVN include joint space preservation and subchondral fracture with changed contour and increased density. Bone scan may show hot uptake before roentgenographic changes are evident. The increased density results from reparative new bone, collapse and condensation of dead bone, marrow fat calcification, and subsequent trabecular thickening surrounding the infarct. Suggested staging based on x-ray, scan, and MRI changes have been proposed (1,17) (Table 14.5).

Most staging or grading systems used to assess the extent of damage use MRI to assess the extent of involvement of the femoral head (<15 percent, 15 to 30 percent, >30 percent) and the extent of sclerosis and cystic change, the degree of head depression and/or collapse, and the degree of acetabular changes (17).

The changes in the contour of the joint result from the failure of the reparative tissues to support the articular surface, with subsequent collapse of the infarcted area. This classically results in a subarticular lucent zone, the crescent sign (18) (Figs. 14.5 and 14.6).

FIGURE 14.4. Avascular necrosis of the femoral head (A) and knee (B). Irregular radiodense subarticular portions of the femoral head and knee indicate dead (and partially reparative) bone.
It should be emphasized that the necrosis involves only bone and bone marrow and not, except in rare cases, the articular cartilage, which receives its nutrition from the synovial fluid. Therefore, the joint space on roentgenograms remains intact. At least in the initial stages of the disease, this radiologic feature clearly distinguishes early AVN from other forms of joint disease, in which the first radiologically evident change is a loss of articular cartilage and joint space narrowing.

Gross examination of a joint surface resected in a patient with early-stage clinical osteonecrosis is likely to reveal fairly intact articular cartilage, although some wrinkling of the surface that marks the edge of the necrotic area will probably be evident. On coronal sectioning, the infarcted zone exhibits a characteristic bright yellow opaque appearance. The infarcted area is usually large, involving 3 cm of subchondral bone and penetrating 2 cm deep (12). If the infarct is recent, a hyperemic zone is present at its margin, to be replaced later by a zone of fibrous scarring.

An infarct heals from the periphery by invading the necrotic marrow with granulation tissue and ensheathing the necrotic trabeculae by a layer of new bone (so-called creeping substitution) identical to that seen in bone repair from other injuries. Some infarcts heal without complication, and such instances are unlikely to be detected clinically because the process is generally asymptomatic. However, some cases are complicated by collapse, perhaps resulting from accumulated “fatigue” microfractures of the necrotic bone trabeculae.

**TABLE 14.5 Stages of Osteonecrosis Based on Roentgenographic Studies**

<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>
<tr>
<td>Ia</td>
<td>Normal radiograph, abnormal bone scan, and/or MRI</td>
</tr>
<tr>
<td>IIa</td>
<td>Abnormal radiograph showing “cystic” and sclerotic changes in the femoral head</td>
</tr>
<tr>
<td>IIIa</td>
<td>Subchondral collapse producing a crescent sign</td>
</tr>
<tr>
<td>IVa</td>
<td>Flattening of the femoral head</td>
</tr>
<tr>
<td>Va</td>
<td>Joint narrowing with or without acetabular involvement</td>
</tr>
<tr>
<td>Vi a</td>
<td>Advanced degenerative changes</td>
</tr>
</tbody>
</table>

*The extent or grade of involvement should also be indicated as A, mild; B, moderate; or C, severe.

**FIGURE 14.5.** Avascular necrosis of the knee. Anteroposterior x-ray of the knee in a middle-aged woman with sudden onset of knee pain. Sclerosis and disruption of the medial femoral condyle is seen (A). A coronal section (B) gross; (C) microscopic] taken through the medial condyle of a patient with osteonecrosis of the knee shows a zone of bone necrosis immediately under the articular surface characterized by an opaque-yellow appearance. Immediately beyond the necrotic zone is a band of hyperemia. (Continued)
FIGURE 14.5. (Continued) Separating the necrosis bone from the overlying cartilage is a gap created by the collapse of the bone trabeculae in the necrotic segment. Microscopically, there is collapse and compression of the dead subchondral bone. A radiolucent space ensues (C, D). Dead bone may adhere to residual viable cartilage and eventually dislodge into the joint, manifesting itself as a loose body (E).

FIGURE 14.6. Avascular necrosis of the femoral head. Roentgenogram (A) and coronal MRI image (B) demonstrate avascular necrosis of the femoral head seen as density sclerosis in A and low signal in B (black arrows). Note the crescent sign (long arrow in A) indicating subchondral collapse, corresponding to the lack of perfect sphericity of the femoral head in B. (Continued)
Size of lesion is important for prognosis; however, the best method of assessing the size of the lesion has yet to be fully elucidated or defined.

Acetabular articular cartilage involvement is an important determinant of disease severity in classification systems. Again, the method to determine this, whether preoperatively or with intraoperative inspection, has not been fully elucidated.

The amount of femoral head depression is a major prognostic indicator of disease progression.

Measurement of the amount of the depressed femoral head that is involved as well as the length of the crescent may not be reproducible.

The location of the lesion may not be as important as size when dealing with large lesions, because lateral lesions are usually large. Medial lesions, although quite rare, are typically small and are associated with the best prognosis.

Idiopathic Avascular, Aseptic Necrosis of the Hip

Mont et al. (17) have recently summarized key points regarding AVN of the femoral head:

- Magnetic resonance imaging is the most sensitive and specific diagnostic method.
- Symptomatology, although important for planning treatment strategies for individual patients, is not a reliable indicator of disease severity because it is quite variable; thus, it should not be part of the classification system.
- A major determinant of prognosis is whether the femoral head is at the precollapse or postcollapse stage.

- Size of lesion is important for prognosis; however, the best method of assessing the size of the lesion has yet to be fully elucidated or defined.
- Acetabular articular cartilage involvement is an important determinant of disease severity in classification systems. Again, the method to determine this, whether preoperatively or with intraoperative inspection, has not been fully elucidated.
- The amount of femoral head depression is a major prognostic indicator of disease progression.
- Measurement of the amount of the depressed femoral head that is involved as well as the length of the crescent may not be reproducible.
- The location of the lesion may not be as important as size when dealing with large lesions, because lateral lesions are usually large. Medial lesions, although quite rare, are typically small and are associated with the best prognosis.

Both nonoperative (lipid-lowering agents, anticoagulants, shock-wave therapy, pulsed electromagnetic fields) and operative treatments (core decompression, bone grafts, stem cell grafts, cementation) have been applied to this puzzling entity (1).
Osteochondrosis/Osteonecrosis

Clinical Syndromes

Osteochondritis Dissecans

Osteochondritis dissecans (OCD) is a lesion of the subchondral bone that may involve partial or total separation of a fragment of the articular cartilage and subchondral bone from the articular surface (20). It can present in skeletally immature children and adolescents (juvenile form) or in skeletally mature adults (adult form).

Classically, the lateral aspect of the medial femoral condyle is affected (Fig. 14.7). Pathologically, this is usually associated with osteonecrosis localized to the subchondral bone fragment. Although the knee is the most common site, this type of subchondral osteonecrosis can occur in other joints, including the capitellum of the elbow, hip, talus, humerus, and patella. Bilaterality has been well documented in the femur. Although it is generally believed to follow a traumatic event with subsequent loss of the blood supply, this is not clearly established. It may be, as previously described, a multifactorial etiology including vascular injury, with biomechanical factors as well.

The occurrence of OCD in twins and in families supports the idea that there may be a genetic predisposition to the disorder (21).

The zone of osteonecrosis may be roentgenographically detectable by an area of sclerosis and a radiolucent linear line, not dissimilar to the crescent sign of AVN of the knee or hip (Figs. 14.5 and 14.6). In osteochondritis dissecans of the knee, this subchondral zone of osteonecrosis may remain anatomically confined to the femoral condyle or in fact be dislodged into the joint, forming a loose body. In fact, the loose subchondral osteonecrotic bone may be the nidus for the formation of an even larger loose body.

Symptoms reflect the various stages of development (Fig. 14.8) of this phenomenon. Sometimes vague, symptoms may include pain, or if the loose body is dislodged, mechanical locking of the joint. Osteochondritis dissecans is most common in men in the second and third decades of life.

Legg–Calvé–Perthes Disease

Legg–Calvé–Perthes disease occurs during childhood and is thought to be due to isolated or multiple episodes of infarction, most likely due to interruption of the medial femoral circumflex artery, absence or occlusion of its lateral epiphyseal branches, and even absence of anastomosis between the circumflex vessels and branches of the obturator artery (22) (Fig. 14.9). The resulting injury results in partial or total necrosis of the epiphysis, with boys being affected four times more frequently than girls. Others have postulated a coagulopathy etiology.

The incidence of Legg–Calvé–Perthes disease has been shown to be increased in the presence of factor V Leiden mutation, in the presence of prothrombin G20210A mutation, in association with elevated levels of factor VIII and in association with protein S deficiency (23).

The intermittent pain and limping associated with Legg–Calvé–Perthes injury is now thought to be due to pathologic fracture of tissue and the ensuing subchondral osteonecrosis. The well-described crescent subchondral line in children, an early radiographic feature of Legg–Calvé–Perthes disease, mimics that seen in the adult

Sites of Osteochondritis Dissecans

![Sites of Osteochondritis Dissecans](image-url)
by some to be a disorder characterized by AVN, which, if complicated by pathologic subchondral fracture, may lead to further damage including resorption of bone and collapse of the femoral head. Numerous clinical correlations with bone necrosis have now been established, and multifactorial effects have been proposed (Fig. 14.10).

**Fat Embolization**

Fat embolism as a cause of osteonecrosis has been suggested clinically for more than 30 years. The support for an etiology of...
osteonecrosis from fat embolization derives from biophysical forces. Fat has a greater viscosity than plasma, and its surface tension may facilitate adherence to arterial walls. It has been speculated that increased blood viscosity or increased arterial wall length or decreased vascular diameter as well as decreased intravascular pressure gradients all may reduce blood flow and potentiate intraosseous fat trigger damage. There are at least three proposed etiologies for fat embolization: the hyperlipidemia associated with fatty liver, endogenous production of lipoprotein, and the destruction of marrow fat. The latter may be a contributing factor in post-traumatic osteonecrosis.

Experimental models have demonstrated that following fat embolism, hypoxia and hypercapnia occur and that chemical mediators such as phospholipase $A_2$, nitrate/nitrite, methylguanidine, and other proinflammatory cytokines are significantly increased (24).

**Corticosteroid-induced Osteonecrosis**

Perhaps the best studied association of osteonecrosis is that seen in association with corticosteroid therapy. In fact steroids have been known to complicate a wide variety of illnesses including steroid treatment for hematologic malignancies, lupus erythematosus, and renal and cardiac transplantation as well as allogeneic bone marrow transplantation.

Although most of these have required long-term steroid therapy, there is increasing evidence that the use of corticosteroids even in short duration may induce or exacerbate the predilection for the development of avascular necrosis of the bone.

First described in 1957, numerous studies have substantiated the risk of corticosteroid intake. Although it was previously thought that large doses of prednisone per day were critical for the development of osteonecrosis, there is much individual variation in susceptibility and, therefore, the extent of use that constitutes a risk is still under debate. A comprehensive study searching for the incidence of osteonecrosis in a prospective fashion revealed that 52 percent of patients with systemic lupus erythematosus had ischemic necrosis in 93 sites with multiple site involvement (25). The hips, knees, and shoulders were most affected.

Although dosages usually considered to be associated with osteonecrosis are $>2$ g of prednisone, or its equivalent, within a period of 2 to 3 months, steroid therapy has been reported to be complicated by AVN with as little as 25 mg of dexamethasone for 7 days, the smallest reported dose being 16 mg for 30 days (1,25). Reports of osteonecrosis have followed not only oral administration but even soft tissue injections of corticosteroids.

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Although the pathogenesis of osteonecrosis is still unknown, much has been learned about corticosteroid-induced osteonecrosis (26,27). Dexamethasone promotes adipogenesis and downregulates osteoblast differentiation. Studies in animal models have shown that dexamethasone shifts the differentiation of bone marrow stem cells from an osteoblast to an adipose differentiation, giving credibility to long-standing hypotheses that fat accumulation...
in the bone is an important culprit in the development of osteonecrosis. With increased fat, there is demonstrable increased intrasosseous pressure and subsequent decreased blood flow. In addition, dexamethasone has been shown to downregulate the expression of osteogenic genes such as type I collagen, RUNX2/cbf1, and osteocalcin (26).

Glucocorticoids also decrease cyclooxygenase-2 (COS-2) and prostaglandin E2 (PGE2) production. The most common site by far for steroid-induced osteonecrosis is the femoral head, followed by the knee, the humeral head, and the distal end of the femur. Other unusual, but well-documented, sites are the talus, capitulum, mandible, and axilla. In steroid-treated lupus, bilateral osteonecrosis is common.

**HIV and Osteonecrosis**

HIV patients have a higher incidence of osteonecrosis than the general population. There has been no association with CD4 cell counts, age, or viral load. HAART treatment of AIDS has been implicated, but HIV-infected patients have multiple risk factors including hypercoagulability, corticosteroid treatments, and altered lipid metabolism.

**Gaucher Disease**

Gaucher disease (GD), the most common lysosomal storage disease and a potentially lethal disorder if fully expressed, is an autosomal recessive disease caused by deficient activity of the enzyme glucocerebrosidase (acid β-glucosidase). As a result of this enzyme defect, the glycosphingolipid substrate, glucosylceramide, accumulates in the monocyte-macrophage system of the bone marrow, spleen, and other organs. It is estimated to affect 10,000 to 20,000 Americans (28), but is most common in the Jewish population, particularly the Ashkenazi Jews. Although considered a rare disorder, milder forms of the disease are encountered frequently, and, in fact, nearly 1 in 835 offspring of marriages between Ashkenazi Jews would be predicted to be homozygous for the condition (29). In this disorder, there is replacement of the marrow by histiocytic-type cells causing numerous skeletal problems including osteoporosis, infarction, and, in some instances, osteomyelitis. Although there are at least three well-recognized forms of the disorder, the adult type of GD often presents with skeletal problems (Table 14.6). It is usually diagnosed in the first and second decades of life and may be associated with a normal life span. In general, when evaluating a Jewish patient with bone pain, splenomegaly, and thrombocytopenia, a diagnosis of GD should be considered.

The disorder is characterized by the abnormal accumulation of glucocerebroside in the lysosomes of reticuloendothelial cells. The deficiency of glucocerebrosidase, an enzyme needed for the degradation of lysosomes of glycolipids, leads to the accumulation of very insoluble glucocerebroside. These accumulate in large cells, and eventually, the proliferation of these cells replaces large segments of the bone marrow. The condition is often diagnosed at tissue pathology unsuspectedly in tissue removed for an orthopaedic procedure such as bone infarction.

There are at least three clinical subtypes of GD, which have been outlined (Table 14.6). By far the most common is type I, in which there is absence of neurologic involvement. The other two are characterized by pronounced neurologic involvement. Type II can often cause death within the first 2 years of life.

Although all cells are deficient in glucocerebrosidase activity in GD, it is a macrophage-type cell that is primarily involved (30). This macrophage is usually a mononuclear cell with abundant cytoplasm characterized by a crumpled cytoplasm (Fig. 14.11). It often proliferates within the liver and spleen, the latter often leading to marked splenomegaly, which causes the presenting clinical picture, thrombocytopenia. Gaucher cells have abundant crumpled cytoplasm, and stain positive with iron and aldehyde groups (periodic acid–Schiff [PAS]), CD68, and acid phosphatase stains (30). Grossly, bone involved in GD has a greasy appearance.

The diagnosis of GD is based on demonstrating markedly low glucocerebrosidase activity in skin fibroblasts or peripheral blood cells. Enzymatic assays to evaluate β-glucocerebrosidase activity in leukocytes combined with molecular analysis is generally considered to be the gold standard for diagnosis. Mutations consistent with GD can be identified in DNA isolated from blood or other tissue as a confirmatory procedure. DNA testing provides a reliable means to identify carriers. Because four common mutations (N370S, L444P, 84GG, and IVS2) account for 95 percent of all nonfunctional Gaucher genes in the Ashkenazi Jewish population, identification of one of these identifies the disease. If all mutations are negative, there is still a chance the patient has another Gaucher mutation (<5 percent) (31).

More than 200 mutations of this gene have been reported as being associated with GD. In the Ashkenazi Jewish population, the predominant point mutation is N370S, a mutation that accounts for approximately 75 percent of the mutant alleles in Jewish patients and approximately 30 percent in non-Jewish patients (30). This mutation predisposes to type I disease and precludes neurological involvement. The L444P mutation is common in the Swedish Norrbottian population, and the homozygous state has a very high association with the neuronopathic variants of GD.

The N370S and 84GG mutations probably originated in a single founder (or progenitor) among the Ashkenazi Jews. Despite considerable uncertainty about the demographic history of Ashkenazi Jews and their ancestors, the available genetic data are consistent with a founder effect resulting from a severe bottleneck in population size between 1100 AD and 1400 AD, and an earlier bottleneck in 75 AD at the beginning of the Jewish diaspora (30). Associated laboratory findings are elevations of serum acid phosphatase, angiotensin-converting enzyme, and hypergamma-globulinemia (28).

The clinical features of type I GD are highly variable, but include anemia, thrombocytopenia with or without bleeding, hepatosplenomegaly without pain or discomfort, and radiologic changes with or without fractures, infarctions, and osteomyelitis.

The bone is often involved in GD due to marrow replacement by macrophages leading to numerous roentgenographically detectable abnormalities, which include abnormal modeling of bones such as Erlenmeyer flask deformities, aseptic necrosis of bones including femoral heads, osteopenia, bone erosions, periosteal reactions, and pathologic fractures (Fig. 14.12). In studies of children with GD, the distribution of fractures most commonly involves the distal part of the femur, the proximal part of the tibia, the base of the femoral neck, and thoracic and lumbar regions of the spine. Other sites such as the proximal humerus, rib, acetabulum, and distal part of the tibia have also been associated with fracture. Bone crises not unlike those described in association with sickle cell disease consisting of pain and sometimes swelling have been noted.
<table>
<thead>
<tr>
<th>Type</th>
<th>Age of Onset</th>
<th>Life Span/Severity</th>
<th>Nervous System</th>
<th>Bone Changes</th>
<th>Thrombocytopenia</th>
<th>Hepatosplenomegaly</th>
<th>Glucocerebrosidase Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Adult nonneuronopathic</td>
<td>First and second decades</td>
<td>Frequently normal</td>
<td>No involvement</td>
<td>Infarcts, aseptic hip necrosis, vertebral compression</td>
<td>Usual, may be prominent</td>
<td>+</td>
<td>Some but much less than normal</td>
</tr>
<tr>
<td>1 in 450 Ashkenazi Jews</td>
<td></td>
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<tr>
<td>1 in 100,000 general population</td>
<td></td>
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<tr>
<td>II. Acute neuronopathic</td>
<td>2–3 mo</td>
<td>Death by 1 y</td>
<td>Occasional</td>
<td>Opioid tolerance, spasticity, neuronal loss prominent in cranial nerves</td>
<td>Uncommon</td>
<td>+/-</td>
<td>Very little</td>
</tr>
<tr>
<td>1 in 100,000 live births</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>III. Juvenile subacute neuronopathic</td>
<td>First year</td>
<td>Slowly progressive; seizures, progressive retardation</td>
<td>Occasional</td>
<td>Infarcts, aseptic hip necrosis, vertebral compression</td>
<td>Uncommon</td>
<td>+</td>
<td>Little</td>
</tr>
<tr>
<td>1 in 50,000 live births</td>
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<tr>
<td>Norrbottian variant in Sweden</td>
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</table>
The osteonecrosis seen in GD may be associated with acute pain (“Gaucher crisis”). Often accompanied by fever, leukocytosis, and an elevated sedimentation rate, it can mimic osteomyelitis. Osteonecrosis usually involves the femoral heads, distal femora, proximal tibiae, and proximal humeri. Often progressive, a risk factor for osteonecrosis in these patients is a previous splenectomy (28). Gaucher osteonecrosis has been associated with hyperviscosity, decreased factor IX, and deficiency of protein C.

MR using T1- and T2-weighted sequences is a valuable, non-invasive diagnostic method for evaluating the severity of bone disease. Both MRI and 99mTc-Sestamibi scintigraphy are reliable tools for assessing the severity of bone marrow involvement in patients with GD (32).

In type I, or the orthopaedic type of GD, symptoms may in fact be mild and not detectable until well into adult life, often in bone marrow evaluations for thrombocytopenia. In these patients, the disease may not be progressive. The splenomegaly associated with Gaucher may be massive and has in the past required splenectomy. However, this may be associated with an increase in bone involvement and further osteolytic and subsequent sequelae such as osteonecrosis.

In addition to osteonecrosis and pathologic fractures of long bones, as previously described, patients with GD may present with other interesting orthopaedic abnormalities including osteomyelitis, kyphoscoliosis due to secondary vertebral collapse, and others with nonspecific bone pain. Some of these patients have been biopsied, revealing culture negative tissue, albeit inflammatory, a condition termed pseudo-osteomyelitis (33). These patients with pseudo-osteomyelitis were characterized clinically by localised tenderness, redness, and swelling often involving the femur and presenting with fever and an occasionally raised sedimentation rate and leukocyte count. The attacks were self-limiting and characterized by a negative culture.

In the patient with so-called bone crisis, roentgenographic imaging techniques may be helpful in localizing lesions. Mechanisms to explain the incidence of pathologic fractures have been postulated. The Gaucher cell infiltrate may lead to mechanical obstruction of the blood supply and subsequent ischemia or mechanical pressure. Alternatively, a lysosomal effect may lead to osteoarticular bone erosion. Ischemia may lead to osteonecrosis, pain, and secondary diffuse osteoporosis, or bone erosions may directly lead to osteopenia.

Historically, therapy had been directed to symptomatic management. Conservative therapeutic approaches include hydration, analgesics, and narcotics for bone pain crises, and orthopaedic fixation of fractures. Splenectomy, either total or partial, had been used although the controversial fear of augmented orthopaedic problems in these patients following splenectomy is a consideration.
Although enzyme replacement therapy (ERT) is effective in reducing visceral and hematologic involvement and complications, its greatest advantage is in the prevention of irreversible skeletal damage (34). Skeletal response to treatment may be slow, but bone crises are much less frequent in ERT-treated patients. The extent to which ERT reduces Gaucher cell infiltration is unclear. Spleenectomy, a mainstay of clinical management in the pre-ERT era, has been obviated by ERT (34). In addition, thrombocytopenia and subperiosteal bleeding (a cause of “bone crisis”) is less frequently observed. Additional benefits of ERT include demonstrable increases in bone mineral density, especially in combination with a bisphosphonate (but not necessarily so in splenectomized patients) (35).

Although joint replacement and other orthopaedic procedures may be of great symptomatic relief, the results of total hip arthroplasty were disappointing. Because the gene for glucocerebrosidase (located on chromosome 1q21) has been characterized and sequenced, enzyme replacement therapy has become a significant advance in the treatment of GD. However, gene therapy is quite expensive. Complicating matters, more than 50 mutations of the glucocerebrosidase gene have been identified, the most common of which are abnormal alleles in N37OS (67 percent) and 84GG (13 percent) (28).

Enzyme replacement therapy first began in 1991 with the recombinant glucocerebrosidase drug imiglucerase (Cerezyme) given intravenously. Oral therapy with Genzyme followed.

Although enzyme replacement therapy (ERT) is effective in reducing visceral and hematologic involvement and complications, its greatest advantage is in the prevention of irreversible skeletal damage (34). Skeletal response to treatment may be slow, but bone crises are much less frequent in ERT-treated patients. The extent to which ERT reduces Gaucher cell infiltration is unclear. Spleenectomy, a mainstay of clinical management in the pre-ERT era, has been obviated by ERT (34). In addition, thrombocytopenia and subperiosteal bleeding (a cause of “bone crisis”) is less frequently observed. Additional benefits of ERT include demonstrable increases in bone mineral density, especially in combination with a bisphosphonate (but not necessarily so in splenectomized patients) (35).

**FIGURE 14.12.** Gaucher disease. Roentgenographic features. (A) Pelvis: there is osteonecrosis of the right femoral head causing collapse and fragmentation. The differential diagnosis includes other causes of ischemic necrosis, such as Legg–Calvé–Perthes disease in a child, or epiphyseal dysplasias. (B) Knee: there is widening of the distal femoral metaphyses, resulting in an Erlenmeyer flask deformity. Other causes of Erlenmeyer flask deformity include thalassemia, diaphyseal dysplasia, and osteopetrosis. Faint areas of increased density, infarction, are present in the femoral shafts.
Appearing as an abnormally low-intensity signal, the displacement of fatty marrow by Gaucher cells is best detected by T1-weighted MRI. Following ERT, the responding bone marrow shows increased triglyceride content and an increase or brightening in the bone marrow signal. Although enzyme therapy has successfully reversed abnormal blood counts, decreased liver and spleen size, and corrected some skeletal abnormalities (35), cost is a factor (several hundred thousand dollars per year for each patient). In recent years, clinical and investigational trials using substrate reduction therapy (SRT) with agents such as miglustat and eliglustat are being evaluated (36).

The value of treatment for asymptomatic patients has not been determined, and general population screening for affected people and carriers is not currently advocated (28).

Additional risks in GD include an increased incidence of cancer, especially hematopoietic in origin. It has been estimated to be as high as a 15-fold risk.

Following bone infarction in GD, as with infarcted bone of other etiologies, tumors, including sarcomas, have been reported (37).

Other storage disorders (e.g., von Gierke disease) and metabolic disorders manifested with Gaucher-like macrophage proliferation (e.g., Niemann–Pick disease) have been less well investigated.

In von Gierke, the most common glycogen storage disease, osteopenia and retarded bone maturation are the most common findings, but multiple growth arrest lines, anteriorly scollied vertebral bodies, fractures, prominent nutrient foramina, overconstriction of long bones, gouty changes, Schmorl nodes, widening of the distal aspects of the metacarpals, and notchings of the medial aspects of the proximal humeri have been reported (38).

In Niemann–Pick disease (a group of sphingomyelin–cholesterol lipidoses), hepatosplenomegaly and foamy histiocytes in the bone marrow, spleen, and lymph nodes are the most commonly encountered clinical phenomena. Niemann–Pick disease is similar to type II GD in its clinical and pathologic manifestations; its diagnosis is established by decreased sphingomyelinase activity in cultured leukocyte and fibroblast extracts (39).

Alcohol

Insofar as alcohol is associated with marked fatty change of the liver, it is not surprising that the etiologic link to osteonecrosis has been through a proposed hyperlipidemia pathogenesis. Although somewhat obscure, the link between alcohol and osteonecrosis is established on clinical grounds and would appear to be one of the common risk factors in alcoholics.

It has been estimated that there is a dose-dependent relationship between alcohol consumption and the risk of developing osteonecrosis with relative risks of 3.3, 9.8, and 7.9 for current drinkers consuming <440, 400 to >1,000, and >1,000 mL/week of alcohol, respectively (1).

Experiments have shown that alcohol treatment decreases osteogenesis while enhancing adipogenesis in a cloned bone marrow stem cell, adipogenesis being a common pathway for several comorbidities producing osteonecrosis.

Mesenchymal stromal cells exposed to alcohol show an enhanced expression of the adipose-specific gene 422 (aP2) and a decreased expression of the type I collagen osteogenic gene. Ethanol may also decrease osteogenesis and increase adipogenesis through the Wnt/β-catenin signaling pathway in part by decreasing intranuclear translocation of β-catenin (40).

Alcohol has additional adverse skeletal effects as described elsewhere, which includes an adverse effect on skeletal remodeling associated with not only osteoporosis but, in some alcoholics, osteomalacia as well.

Sickle Cell Disease

The osteonecrosis seen in association with sickle cell anemia is thought to be due to intravascular stasis and thrombosis following polymorphonuclear leukocyte-induced alteration of endothelial cells (for sickle cell disease, see Chapter 12). Altered endothelial cells may lead to preferential adherence by sickle cells with subsequent damage and intimal cell proliferation.

Osteonecrosis in this setting may be seen in multiple sites, particularly around the hips, knees, and shoulders. Avascular necrosis of the femoral head is well described. Unlike osteonecrosis of the hip due to other etiologies, 91 percent of asymptomatic hips with osteonecrosis in patients with sickle cell disease eventually become painful, and 77 percent collapse (41). The effect of sickle cell anemia on the skeleton is diverse and includes not only osteonecrosis but also osteomyelitis including unusual infections such as Salmonella. In addition, silent ischemic episodes are suspected.

Decompression Sickness (Caisson Disease)

When air is breathed under increased ambient pressure, as is the case in commercial and sport diving, inert gases such as nitrogen dissolve in the tissue and blood, reaching a saturation equilibrium (42). On rapid accession to sea level (“decompression”), the inert gases may come out of solution to form intravascular bubbles. These bubbles may serve as emboli and cause significant, if not life-threatening, complications. Manifestations of these decompression episodes were first described in the 19th century in caisson workers who used platforms in deep water or deep mud construction where the compressed air was used to exclude water and mud. The risk of decompression sickness is minimal with working pressures below 11 pounds per square inch gauge (psig) pressure. Significant risk of developing osteonecrosis occurs at pressures >17 psig.

The clinical manifestations of decompression sickness include deep pain in the joints, made worse by exercise, the so-called bends. Bone infarction is most commonly reported in the humerus, femur, and tibia. In deep sea divers, in contrast to other causes of osteonecrosis, the humerus is more frequently affected. In decompression osteonecrosis, the knee and elbow are most often involved, rarely so in deep sea divers. Additional symptoms include chest pain, dyspnea, confusion, and other neurologic symptoms, and even seizures. The condition may progress to shock and death.

Roentgenographic evidence of caisson disease may be evident as early as 4 months, but clinical symptoms may not develop for years.

The treatment of decompression disease is to return to sea level gradually. It is routine practice among commercial and sport divers to follow guidelines for ascent. These time tables and graduations to different sea level pressures allow for decreased bubble size, permitting resorption of potentially damaging embolic-type gases. It is interesting to note that decompression sickness has been reported in dives as shallow as several meters.

From a pathophysiologic point of view, when a diver breathes air under increased pressure, increased quantities of oxygen and nitrogen are inhaled. Whereas oxygen is used in tissue metabolism,
nitrogen, physiologically inert, is not. The latter gas is much more soluble in fat than in water. Supersaturation may ensue following rapid ascent, liberating free gases and triggering embolic arterial venous and lymphatic blockade, leading to significant organ dysfunction and even compartmental syndromes.

An alternative hypothesis for dysbaric osteonecrosis postulates that necrosis occurs not from a primary embolic or compressive effect of nitrogen bubbles on the bone vasculature, but rather as a secondary injury to narrow fat by rapidly expanding nitrogen gas that initiates local and possibly systemic intravascular coagulation in the form of fibrin platelet thrombi. Increased fibrin degradation products, accelerated platelet turnover, and decreased AT III activity have all been described. As with other forms of osteonecrosis, MRI evaluation has led to classification schemata and staging (43).

In modern times, the economic necessity for oil companies to maintain pipelines and offshore rigs has sent scores of divers routinely to depths of a thousand feet, requiring prolonged compression for as long as a month at a time (44). This has led to the development of saturation diving complexes. Located on the ship’s deck or rig, and looking like mini space stations, divers are sealed inside while the air pressure is increased until it matches the pressure at the job’s working depth. The deeper the job, the more helium is used, since helium mitigates the risk of nitrogen narcosis. Helium is easier to breathe under pressure because of its low density and is more quickly flushed from organs and tissues than heavier gases. So our modern appetite for oil is expending research and understanding of decompression sickness.

## Gout and Osteonecrosis

The relationship between gout and osteonecrosis of the bone is unclear (44). In 1955, Mauvoisin et al. (45) were the first to report on the occurrence of aseptic necrosis (avascular necrosis) of the femoral head in a patient with clinical gout. Subsequently, a number of authors have reported an increased incidence of gout and/or hyperuricemia in patients with femoral head necrosis (46).

The etiologic relationship between gout, hyperuricemia, and AVN of a joint or bone has yet to be revealed. Hunder et al. (47) reported the difficulty in determining whether a particular case is truly idiopathic because the rare association of the femoral head would implicate a multifactorial cause. They also stated that the lack of a prospective study revealing urate deposition in the tissue prior to the start of AVN further complicates the cause and effect relationship (47).

Giacomello et al. (48) proposed that increased intra-articular effusion caused by the gouty inflammatory reaction might increase intra-articular pressure exceeding venous and arterial pressure, resulting in thrombosis of vessels and necrosis of bone similar to that mechanism used to describe avascular osteonecrosis of the femoral head.

The most probable relationship is that gout is a secondary phenomenon. The necrotic bone in the femoral head may alter the surrounding tissues by lowering the pH, favoring the deposition of monosodium urate crystals (49,50). Seegmiller et al. (50) showed that in avascular tissue, glycolysis is the principal source of energy, leading to lactic acid production and a resultant lower pH. Therefore, one can hypothesize that avascular regions of tissue should be more prone in the presence of urate deposits.

It has been suggested that a high serum uric acid level as well as a high concentration in the tissue fluid may be a prerequisite for gout to precipitate. Osteonecrosis probably reduces the pH at certain bone sites, further creating a more favorable environment for the gouty tophi to deposit.

## Inflammatory Bowel Disease

Non–corticosteroid-associated osteonecrosis of the femoral head has been documented in inflammatory bowel disease (51). The presence of fibrin microclots has been postulated as etiologic factors due to hyperviscosity, increased generation of thromboplastin, hyperfibrinogenemia, thrombocytosis, and hypercoagulability. Hypercoagulability may be due to malabsorption-associated depletion of vitamin K and decreased protein C and protein S.

## Pregnancy

Although the etiology is not clear, osteonecrosis may complicate pregnancy (24). Oral contraceptives and hyperlipoprotein states have been implicated as well as fatty livers.

## Other

Other clinical associations with avascular osteonecrosis include bone marrow and renal transplantation (52) and that seen in association with chemotherapy (53) and unstable slipped capital femoral epiphysis.

Osteonecrosis of the jaw has been associated with both the intravenous and oral use of bisphosphonates in the treatment of osteoporosis. Presenting lesions are usually a nonhealing extraction socket or an exposed jaw bone (54) (see Chapter 3).

## Genetics of Osteonecrosis

The occurrence of idiopathic AVN in twins and families implies that genetic factors are involved (55). The search for genetic risk factors for osteonecrosis has focused on coagulation defects and collagen genes. Of note are the following:

- Patients with familial AVN have been found to have mutations in the collagen 2A1 gene.
- The factor V Leiden mutation, a common risk for thrombophilia, and polymorphism of the prothrombin gene G21210A, a common risk factor for thrombosis, have been associated with AVN.
- Genes involved in the pharmacokinetics of antileukemic medication, such as in the treatment of acute lymphoblastic leukemia, may render patients vulnerable to AVN.
- Polymorphic variants of alcohol-metabolizing enzymes may render a subset of patients more susceptible to alcohol-related AVN.
- Bone morphogenetic protein 6 (BMP6) and annexin A2 genes have been implicated in osteonecrosis in sickle cell anemia (55).

## Thrombophilia and Hypofibrinolysis

A plethora of coagulation defects are suspected to contribute to the pathogenesis of nontraumatic osteonecrosis, and they are enumerated in Figure 14.13. In the case of thrombophilia, disturbances are associated with an increased propensity to form clots (56). With hypofibrinolysis, there is a decreased ability to lyse clots (57).
Orthopaedic Pathology

Thrombophilic disorders associated with osteonecrosis include (Fig. 14.13):

- Protein C deficiency. With deficient protein C, the prothrombotic clotting factor Va is insufficiently expressed, and increased coagulation occurs.
- Resistance to activated protein C (APC). This commonly occurring clot disorder results from mutations of the factor V Leiden gene. Mutations prevent the appropriate interaction of APC to factor V.
- Protein S deficiency. With deficient protein S, the prothrombotic clotting factor Va is not adequately suppressed, the result of which is increased coagulation in veins and arteries.
- Anticardiolipin antibodies. These antibodies are a class of antiphospholipid antibodies strongly associated with thromboembolic events. Lupus erythematosus is associated with high levels of related antibodies.

Hypofibrinolytic disorders include abnormalities in the interaction between tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI), an interaction that helps control fibrinolysis. High levels of lipoprotein A have been associated with inhibition of fibrinolysis.

The action of thrombophilic or hypofibrinolytic events may lead to osteonecrosis by the effect of persistent thrombi on venous drainage of bone. With the blockage of venous drainage and arterial flow continuing, venous pressure in the "closed" compartment of bone may rise, leading to reduced arterial perfusion, anoxia, and osteonecrosis (Fig. 14.10).

**Sarcoma Arising in Bone Infarction**

Rarely, a sarcoma may arise at a bone site that has undergone infarction. The cases have been reported throughout a wide range of adult life (essentially third through ninth decade). Blacks are disproportionately represented. An identifying underlying etiology to the osteonecrosis is not always identified. Alcohol-related, sickle cell disease, steroid use, fracture, and dysbaric osteonecrosis have been described. Most patients have multiple bone infarcts.

The femur is most commonly involved, followed by the tibia. Infarct-associated sarcoma almost always involved metaphyseal or metadiaphyseal regions of the appendicular skeleton, especially around the knee. The epiphysis, a common site for ischemic necrosis, is a rare site for infarct-related sarcoma. Pain is almost always present and may be of long-standing duration. The most common histologic type of sarcoma is a malignant histiocytyoma followed by osteosarcoma (Fig. 14.13). Angiosarcomas have been rarely identified (58).

The survival rate is poor, with only 20 percent of one series surviving 5 years (59). Ensuing metastatic disease is the rule.

The etiology of infarct-associated sarcomas is not known. The interval between infarction and sarcoma is usually a decade or longer, similar to the long latency period of radiation-induced sarcoma.

MRI can be helpful in diagnosis. In osteonecrosis, both T1- and T2-weighted images should show a low signal centrally, and often delineated in its perimeter by a fine dark line. In infarct-associated malignant fibrous histiocytyoma (MFH) sarcoma, the diaphyseal cortical erosion not present in typical cortical preserving osteonecrosis is detectable by MRI.

Radiation

Radiotherapy is one of the most widely used treatments for cancer today and has been estimated to have been used in half a million people in the United States in 1990 (60).

DNA is thought to be the target of the cytotoxic effects of radiation, and, although there are differences in cellular sensitivity, too much radiation has adverse effects on bone. These include the retardation of growth, the development of osteonecrosis, structural weakening and fracture (61), and sarcoma. Radiated bone is thought to be more prone to infection and fracture with abnormally slow healing (62). Injuries have been reported in the epiphysis (altered chondrogenesis), metaphysis (altered evolution of endochondral ossification), and the diaphysis (altered periosteal bone modeling) (63).

Radiation injury is dose dependent. A threshold of injury appears to be reached at about 3,000 rads, with cell death at 5,000 rads. Damage has been considered more severe with orthovoltage radiation than megavoltage radiation, which is in more common clinical use today.

Much has been learned from catastrophic radiation events. At whole body–absorbed doses, chromosomal aberrations (even in asymptomatic individuals) can be found at 0.15 Gy (Gy, the gray, being the international unit of measurement for the absorbed dose; 1 Gy = 100 rad) (64). Nausea and vomiting occur at 2 Gy in 50 percent of patients. At 6 Gy, there is 100 percent mortality due to bone marrow failure in the absence of medical treatment. Death is assured within 72 hours at >30 Gy.

At dosages used in clinical medicine, growth-related disturbances include scoliosis, kyphosis, and damage to growth plates as seen in hyperplasia of the ilium and the development of osteochondromas (65) in irradiated fields in childhood. Doses between 1,600 and 6,425 rads are thought to produce this effect in children, but lower doses have been reported. At risk are skeletal fields in sites of irradiation for childhood abdominal tumors such as Wilms tumor. Skeletal effects are seen with the younger the age and the greater the radiation. Most severe changes occur when irradiation takes place before the age of 2 years. Spine changes are best described and include decreased vertebral height, end plate irregularity, and both beak- and hump-shaped vertebrae, mimicking spondyloepiphysal dysplasia (66).

Bone growth retardation from radiotherapy has been quantitated. Most pronounced in the very young and those during the adolescent growth spurt, height can be affected 7 to 8 percent in standing or approximately 13 cm (67).

Radiation-induced osteochondroma can develop in any bone and as early as 3 years following radiation. The average latent period is about 8 years, several years shorter than the latency period for developing radiation-induced sarcoma. The incidence has been estimated between 2 percent and 14 percent (66). Doses have been between 125 and 6,345 rads, an admittedly broad range. The autoradiographic localization of the bone-seeking agent thorium X at the growth line of the induced osteochondroma supports a causative effect of radiation (68). Extremely rarely, low-grade chondrosarcomas have been reported to arise in radiation-induced osteochondromas (69).

The most commonly observed effect of radiation on bone is an inflammatory reaction initially described by Ewing termed "radiation osteitis," now considered a nonspecific pathologic process. Most clinically significant is the development of osteonecrosis. Intense high-level radiation may cause immediate cell death involving bone marrow and bone. Less intense radiation may lead to a delayed observation of osteonecrosis. Even less radiation leads to transient changes with recovery. Thus, radiation osteonecrosis may be seen following either a sufficiently large dosage as a direct toxic insult or after a prolonged exposure to lower dosage.

The mechanism of cell death in radiation injury is the result of the production of free radicals (Fig. 14.14), with resultant damage to DNA and reproductive or mitotic death (70). Coupled with this cytocidal effect is the accompanying inflammation with its associated production of oxidized fatty acids and free radicals, which also damage tissue. Damage to blood vessels also is a contributory insult.

In addition, the widespread use of radiotherapy in treating primary and secondary musculoskeletal tumors and tumors in the radiation field of bone have led to the observation of fractures of bone in irradiated fields (71). Sugimoto et al. (71) have quantitatively analyzed the histologic and mechanical properties of irradiated cortical bone. After a single dose of 50 Gy of electron beam to the rabbit tibia, synchronous but reversible changes over 1 year were noticed, which included decreased bone strength, bone formation, and marrow cellularity. Bone porosity increased but recovered. Although osteocyte morphology was not significantly changed (Fig. 14.15), others have reported decreased osteocyte counts (72). They concluded that changes are reversible at this level of radiation.

In further studies of radiation on cortical bone, loss of cells in haversian canals was evident as was capillary injury (dilatation) and abnormal resorption by osteoclasts (70) at 4 weeks following irradiation. Abnormal osteoclast resorption was not coupled effectively with new bone formation, leading to cortical bone porosity. Recruitment of osteoclasts from nonirradiated bone or by local tissue factors was suggested. Radiated bone showed decreased cellularity of all skeletal tissue cells: endothelial cells, pericytes, perivascular mesenchymal cells, osteoclasts, osteocytes, and osteoclasts. Most radiation injury, and particularly that to the osteoblast progenitor cells, was considered vascular in origin.
Loss of mechanical strength with irradiation can be attributed in part to the concomitant development of bone resorption and depressed bone formation, the latter linked to bone marrow injury— the source of osteoblasts (71).

Conversely, fractures may be tumor related (“pathologic”), creating the clinical dilemma of when to initiate appropriate radiation therapy of a tumor in a fractured bone. Although delaying radiation of tumor-related fractures may lessen the short-term deleterious effects on fracture repair, there may be no significant advantages in the long term (62). In general, radiated fractures show a smaller and weaker callus, impaired endochondral ossification in callus, delayed union, and impaired vascularization (77).

Although osteonecrosis has been observed in the treatment of malignant tumors, especially lymphomas, when adjuvant combined radiation and chemotherapy has been used, it has also been reported in adjuvant treatment without radiotherapy (78). The concomitant role of steroids in inducing osteonecrosis in some of these cases is not clear, but may be additive in its effect (79).

Radiation after effects in the treatment of osteosarcoma and other tumors include:

- Telangiectasias
- Intense fibrosis
- Atrophy of normal cellular tissue
- Disappearance of fat
- Endarteritis obliterans (73)

There appears to be a relative susceptibility of different bone elements to radiation injury. Osteocytes, postmitotic differentiated cells, are relatively radioresistant and can sustain high doses of ionizing radiation without cell death (74). Osteoclasts are relatively radioresistant. Osteoblasts are more radiosensitive (75). Marrow cells are radiosensitive, but at least partially recoverable, although less quickly. Megakaryocytes appear less efficient in regenerating after radiation (76). Above 5,000 rads, all marrow elements may fail to regenerate. Osteoclasts, the bone resorption component of tissue bone remodeling, appear more resilient in their recovery than that of osteoblasts, the bone formation component, a precarious biologic circumstance resulting in bone loss (72).

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Radiographically, radiation injury changes are nonspecific. However, bone remodeling associated with radium deposition can

**FIGURE 14.14.** Hypothetical mechanism of irreversible radiation-induced injury to haversian bone. In the early-to-intermediate phase, mediation is chiefly by inflammatory stromal reactions and perhaps by some direct cell damage. Injury in the intermediate-to-late phase is mediated chiefly by reproductive (mitotic) death of the dividing cells and by microvascular damage. Both the stromal reactions and the reproductive death are considered to be responsible for the damage to the microvasculature. Clinical manifestations of radiation-induced osteopathy are considered to be the results of various combinations of these pathological processes and probably of others as well. (Reprinted from Takahashi S, Sugimoto M, Kotoura Y, et al. Long-term changes in the haversian systems following high-dose irradiation. J Bone Joint Surg Am. 1994;76:722–737, with permission.)
lead to roentgenographically detectable sclerotic areas of the epiphyses of long bones.

Bone scans have been studied following radiation injury. The effect is thought to be increased in the immediate postirradiation period, perhaps secondary to inflammation-related hyperemia. Subsequently, a decreased scan is expected, a phenomenon attributed to either vascular injury (vasculitis, vascular occlusions) or osteoblast depression limiting mineralization activity, the two major determinants of a hot bone scan. The effect is thought to be dose related, with 60 percent of patients showing decreased uptake with radiation above 4,500 rads (80). Decreased scan uptake after radiation injury may persist for many years.

The bone suppressive effects of radiation have been therapeutically. In treating the heterotopic bone formation that occurs following some cases of hip arthroplasty, studies have shown success with low-dose radiation (less than 2,000 centigray). Effects are best seen prophylactically within 4 days of surgery (81) in carefully selected patients at known high risk for this postsurgical complication. Experimental evidence that irradiation in the first 4 days after implantation prevents demineralized bone matrix from evolving into roentgenographically detectable bone has substantiated this effect (82).

The effects of radiation have been historically recorded by studying industrial exposure to radium salts. The use of radium salts in illuminating watches by industrial workers who had oral brush contact is a classic description of industrial-related injury (83). These, mostly young, women working in the 1920s in clock companies were taught to tip the tiny brushes between their teeth to shape the bristles into the finest points. The paint on the brushes was not regular paint, but radium paint, used for its property to glow in the dark. By the end of the 1920s, dozens of women in plants in Connecticut, Illinois, and New Jersey had died of the radium exposure. However, other uses of radium salts as, for example, medical treatment for a wide range of disorders, including hypertension and arthritis, have been well described (84). The luminous dial workers were particularly exposed to the hazards of radiation in that the forms of radium included half-lives exceeding that of the normal human life span, thus exposing themselves to a disproportionate amount of radiation. In addition, radium, unlike the x-rays of radiation, emits alpha particles, which are more destructive in tissue (84).

Sharpe (85) has described the morphology of bone and marrow infarcts in chronic industrial radium intoxication injury dating back from a third to half a century. Changes include a microscopically detectable granular basophilic alteration of the bone within cortical and cancellous trabeculae obliterating the normal lamellar appearance on polarized light microscopy. The extent of this granular basophilia, thought to indicate infarction, varies from part of an osteon to nearly the entire cortical thickness of a large tubular bone. Periosteal new bone is spared. The marrow is replaced by sparsely cellular fibrous tissue admixed focally with fragments of necrotic bone or bone debris. Hematopoietic tissue, considered regenerative, is focally seen in marrow fibrosis areas. Sharpe (85) concluded that the injury process is cumulative and continuous, and local blood supply and local osteogenic potential not sufficient to compensate completely, unlike infarcts of other etiologies. Others have described considerable calcification of marrow fat (84).

The effects of radiation on bone grafts have also been studied. Allografts gamma-irradiated to minimize the risk of infectious disease have been found to impair material properties of the bone. Most gamma radiation damage is thought to be induced by the production of damaging free radicals (86). Radiation also alters the number of undifferentiated stem cells available for recruitment, inhibits neovascularity, alters cell signaling pathways, disrupts the normal osteoblast/osteoclast remodeling events, decreases normal collagen synthesis, damages endothelial cells, and inhibits osteoblast differentiation (87).

**Postirradiation Sarcoma**

The development of bone sarcomas following irradiation is well known. In fact, radiation-induced murine osteosarcoma is a model for the evaluation of genetic molecular pathways to malignant...
transformation. In 1929, Martland (83) first recognized the industrial hazard of radiation when the osteosarcomas appeared after ingestion of radioactive radium. Rizzoli et al. (103) reported the clinical application of x-rays (91).

The carcinogenic effect of radiation may be dose dependent, reaching a 40-fold increased risk after doses of more than 6,000 rads (92). It has been documented at a median total dose of 3,600 cGy (1,600 to 11,200), with an interval from radiation to detection of 13.2 years (3.4 to 22.8 years) (93) in Europe and with an average latency period of 14.3 years in the United States (94). There appears to be no difference between megavoltage radiation and orthovoltage radiation in producing sarcoma.

Clinically, patients usually develop a palpable tumor of the soft tissue, but nonspecific swelling or pain may be the only clinical finding. Both soft tissue and bone sarcomas have been described. The most frequent histologic types are, in decreasing order, osteosarcoma, MFH, and fibrosarcoma. However, chondrosarcoma and small cell tumors (lymphoma and Ewing) have been described (94). The longer the time interval between the index tumor and postradiation, MFH, and fibrosarcoma. However, chondrosarcoma and small cell tumors (lymphoma and Ewing) have been described (94). The longer the time interval between the index tumor and postradiation sarcoma (PIS) to be 0.03 to 0.8 percent, comparable to mortality risks of chemotherapy, and general surgery and anesthesia.

The prevalence of secondary tumors after radiotherapy of Ewing has been estimated at 5 to 20 percent of patients with 20 years of follow-up (89).

Criteria for the diagnosis of PIS have been proposed: (a) prior history of radiotherapy, (b) microscopic or roentgenographic evidence that there is initially no malignancy, (c) development of the second primary tumor in irradiated field, (d) long latent period of several years, and (e) histologic proof of sarcoma.

Bone Marrow Edema Syndrome

A plethora of terms have been used to describe an interesting group of clinical syndromes characterized by pain, subtle, if any, radiographic changes of osteolysis, increased uptake on bone scan; and, often, clinical recovery. The histopathology of these syndromes is not well described in the literature, but does support a transient bone injury such as microscopic fractures (102), transient ischemia, or a reversible episode of necrosis (103) (see Fig 4.66). Attempts to distinguish and define them clinically and by imaging techniques continues. Transient osteoporosis and the bone marrow edema (BME) syndrome are usually self-limited, may have joint pain, resolve within a year, and, unlike AVN, do not have a zone of demarcation on MRI imaging (104). Transient osteoporosis, which may become migratory by shifting from one bone or joint to another, is distinguishable from the BME syndrome by imaging evidence of osteopenia. RSD is characterized by pain, dysesthesias, and skin changes.

The prognosis in radiation-induced sarcoma is poor. At the Rizzoli Orthopaedic Institute in Bologna, long-term survivorship was increased in patients if their postradiation sarcoma was treated with surgery combined with chemotherapy (96). Their patients had had a mean radiation exposure of 33 Gy, and after a mean of 15 years developed tumors, most commonly in the femur and pelvis. Osteosarcomas were associated with the best prognosis. Unlike conventional osteosarcoma, the response to chemotherapy as assessed by degree of chemotherapy-induced tumor necrosis does not have prognostic significance (97). Facial and extremity sites offer a better prognosis than the pelvis, vertebral column, and shoulder girdles.

For obvious reasons, radiation therapy for benign tumors should be limited to those not appropriately treated by surgery or other means. Other factors carrying adjuvant risk are genetic predisposition, family history, and chemotherapy. Hereditary conditions predisposing including neurofibromatosis and hereditary forms of Wilms tumor and retinoblastoma.

Bone Marrow Edema Syndrome/Transient Osteoporosis/Migratory Osteoporosis/Reflex Sympathetic Dystrophy

Bone Marrow Edema Syndrome

The BME syndrome is a transient condition of unknown etiology characterized clinically by pain without a history of trauma (105). Most frequently seen in bones around the hip, the knee, ankle, and foot may be affected. Imaging typically shows regional osteopenia and increased uptake on the bone scan. MR shows findings consistent with nonspecific marrow edema: decreased T1 signal and increased T2 signal and hyperintensity on short inversion-time

| TABLE 14.7 Types of Radiation Sarcoma Based on Irradiated Sites and Sites of Radiation-induced New Tumor |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Site of Radiated Primary Tumor | Site of Radiation Tumor |
| Soft tissue | Soft tissue |
| Soft tissue | Bone |
| Bone | Soft tissue |
| Bone | Bone |

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areas subject to a noxious event may be increased as much as tenfold.

Although the condition usually resolves spontaneously, attempts at treatment have been both surgical (core decompression) and medical with agents such as Iloprost (109). Iloprost, a stable prostacyclin analogue used in the treatment of the ischemia associated with diabetes and peripheral vascular disease, is aimed at correcting the presumptive vascular ischemia of this condition. Iloprost has also been used in RSD (110).

**Transient Osteoporosis**

Most agree that “transient osteoporosis” is a variant of the BME syndrome. Purists distinguish it by its imaging findings of osteopenia and occasional migratory pattern (“migratory osteoporosis”) (111). There is little on reported histologic grounds (which have been infrequently documented) to distinguish the two. The condition has been described in pregnancy in which it can be migratory. Supportive care is the rule because it is transient and seemingly refractory to medical treatment (112). Pain is usually progressive, worse during weight bearing or absent during rest. Distinctions with frank AVN can be drawn (Table 14.8).

### TABLE 14.8 Distinguishing Features of Transient Osteoporosis and Avascular Necrosis of the Hip

<table>
<thead>
<tr>
<th></th>
<th>Transient Osteoporosis</th>
<th>Avascular Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>200/y</td>
<td>1,500/y</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>3:1</td>
<td>Equal</td>
</tr>
<tr>
<td>Age, mean</td>
<td>44 y</td>
<td>30 y</td>
</tr>
<tr>
<td>Occurrence in children</td>
<td>Extremely rare</td>
<td>Equivalent to Legg-Calvé-Perthes disease</td>
</tr>
<tr>
<td>Pregnancy association</td>
<td>Yes, last trimester</td>
<td>Rarely</td>
</tr>
</tbody>
</table>
| Etiology                    | Unknown; may be variant of reflex sympa-
|                            | thetic dystrophy or avascular necrosis  | Mechanical interruption of circulation to femoral
|                            |                                        | head                                            |
| Laterality                  | Unilateral, may be recurrent           | Bilateral in more than 50% of patients           |
| Onset of symptoms           | Acute                                  | Insidious                                        |
| Symptoms                    | Pain with weight-bearing antalgic gait, disproportionate functional disability | Pain at rest, limp (late finding)                |
| Imaging findings            |                                        |                                                  |
| Radiography                 | Osteopenia at 4–6 wk                   | Sclerosis, mottled radiolucency, crescent sign, collapse of femoral head |
| Bone scanning               | Diffuse, homogeneous lesions: increased uptake of isotope | Lesion more localized, may present with photopenic area |
| Magnetic resonance          | Diffuse bone-marrow-edema pattern, signal intensity decreased on T1- and increased on T2-weighted images | Focal lesion, anterosuperior region of femoral imaging head; decreased signal intensity on both T1- and T2-weighted images; double-line sign |
| Prognosis                   | Spontaneously resolves within 6–8 mo without sequelae; prognosis more guarded in pregnant patients | Progressive in 70%–80% of patients, usually leading to collapse of femoral head and end-stage degenerative joint disease |
| Treatment                   | Protected weight bearing and treatment of symptoms | Early operative intervention generally recommended |

Complex Regional Pain Syndrome;(Reflex Sympathetic Dystrophy, Algodystrophy; Sudeck Atrophy)

The complex regional pain syndrome (CRPS) is a syndrome that remains enigmatic. Two types have been described:

CRPS type I is a disabling condition that can develop spontaneously or after an injury or surgery. It is characterized by severe pain and a combination of sensory, autonomic, motor, and dystrophic symptoms (110).

CRPS type II develops after a definitive nerve injury.

Classic symptoms of CRPS type I are pain and swelling of the involved extremity often associated with dysesthesia and sympathetic system autonomic dysfunction (cyanosis, skin mottling, coldness, hyperhidrosis). Osteoporosis (Sudeck atrophy), muscle atrophy, and joint contractures can evolve. The histopathology has been infrequently documented, but, where so, is similar to that seen in the BME syndrome and transient osteoporosis (see Fig. 4.66), and is frequently documented, but, where so, is similar to that seen in the BME syndrome and transient osteoporosis (see Fig. 4.66), and is consistent with an ischemic or microfracture event. Treatment of this usually spontaneously remitting condition has been an evolving, and often frustrating, science (110). Physical therapy to break a vicious cycle of disuse, steroids, electrical nerve stimulation, calcitonin, calcium channel blockers, regional anesthesia, α-sympathetic blockers, and operative sympathectomy have all been used. Illo-prost, as with the treatment of the BME, has been used. Amputation in severely refractory and painful cases has its advocates (113). The etiology of RSD remains obscure, and thus medical and surgical treatments are often frustrating and scientifically unproven (114).

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