CHAPTER

43

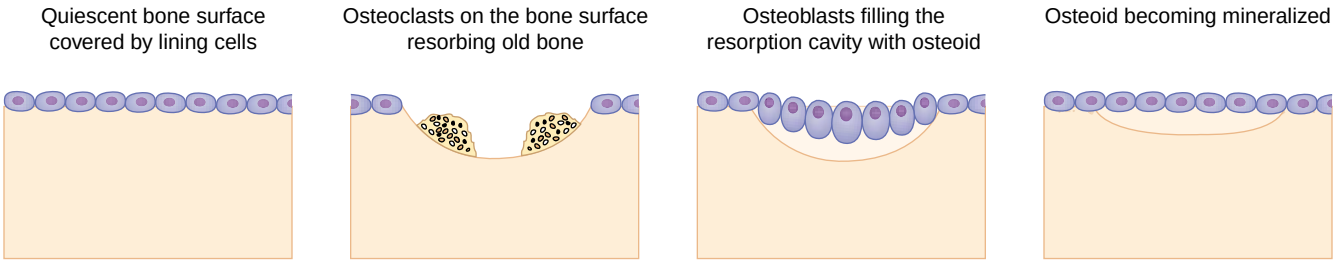
Alterations in the Skeletal System: Metabolic and Rheumatoid Disorders

The skeletal system provides the basic framework that supports the body, protects its organs, and provides for movement. For example, the bones of the lower extremities act as a pillar when we stand, and the ribs provide a cage that supports and protects our heart and lungs. Joints hold the bones of our skeleton together, making movement possible. This chapter focuses on two types of skeletal disorders: metabolic bone disorders, which disrupt bone integrity, and joint disorders, which disrupt mobility.

METABOLIC BONE DISEASE

Bone integrity depends on a process of bone resorption and formation, or bone remodeling, which is continuous throughout life. In the adult, approximately 25% of cancellous or spongy bone is replaced each year, compared with 3% of compact bone.[1] In the adult skeleton, bone remodeling proceeds in cycles that involve resorption of old bone by osteoclasts and subsequent formation of new bone by osteoblasts (Fig. 43-1). The sequence of bone resorption and bone formation is activated by many stimuli, including the actions of parathyroid hormone (PTH) and calcitonin. It begins with osteoclastic resorption of existing bone, during which the organic (protein matrix) and the inorganic (mineral) components are removed. The sequence proceeds to the formation of new bone by osteoblasts. In the adult, the length of one sequence (*i.e.*, bone resorption and formation) is approximately 4 months. Ideally, the replaced bone should equal the absorbed bone. If it does not, there is a net loss of bone. In the elderly, for example, bone resorption and formation no longer are perfectly coupled, and bone mass is lost.

There are three major factors that influence bone remodeling: (1) mechanical stress, (2) extracellular calcium and phosphate levels, and (3) hormones, local growth factors, and cytokines. Mechanical stress stimulates osteoblastic activity and formation of the organic matrix. It is important in preventing bone atrophy and in healing fractures. Bone serves as a storage site for extracellular calcium and phosphate ions. Consequently, alterations in the extracellular levels of these



■ **FIGURE 43-1** ■ The process of bone resorption by the osteoclasts and subsequent bone formation by the osteoblasts.

ions affect their deposition in bone (see Chapter 6). Blood levels of calcium and phosphate are regulated by PTH and calcitonin (see Chapter 41). PTH promotes bone resorption, and calcitonin inhibits bone resorption.

Osteoclasts and osteoblasts have their origin in the bone marrow and the periosteum (see Chapter 41).[1] The osteoblasts, which are bone-building cells, originate from osteoprogenitor cells in the periosteum and the stromal or supporting cells within the marrow cavity. The osteoclasts, which are bone-resorptive cells, are a member of the hematopoietic monocyte/macrophage family. However, the development of osteoclasts from their monocyte/macrophage precursors cannot take place unless stromal-osteoblastic cells are present. The differentiation and function of osteoclasts and osteoblasts are regulated by chemical messengers, including colony-stimulating factors (CSF) and other cytokines (see Chapter 8). Interleukin-6, which is produced in response to systemic hormones such as PTH and vitamin D, stimulates the early stages of osteoclast development. Interleukin-6 is thought to be involved in the abnormal bone resorption associated with Paget's disease.

Recent evidence suggests that an interaction between a chemical messenger called the *RANK ligand*, which is produced by the stromal/osteoblastic cells, and RANK receptors on the macrophage/osteoclastic precursor cell is essential for the differentiation and proliferation of osteoclasts (Fig. 43-2). There also is evidence of a blocking molecule called *osteoprotegrin* (OPG) that can prevent the RANK ligand from binding to the RANK receptor, thus inhibiting the formation of osteoclasts. It is now believed that dysregulation of the RANK ligand/receptor pathway plays a prominent role in the pathogenesis of bone diseases such as osteoporosis.[2]

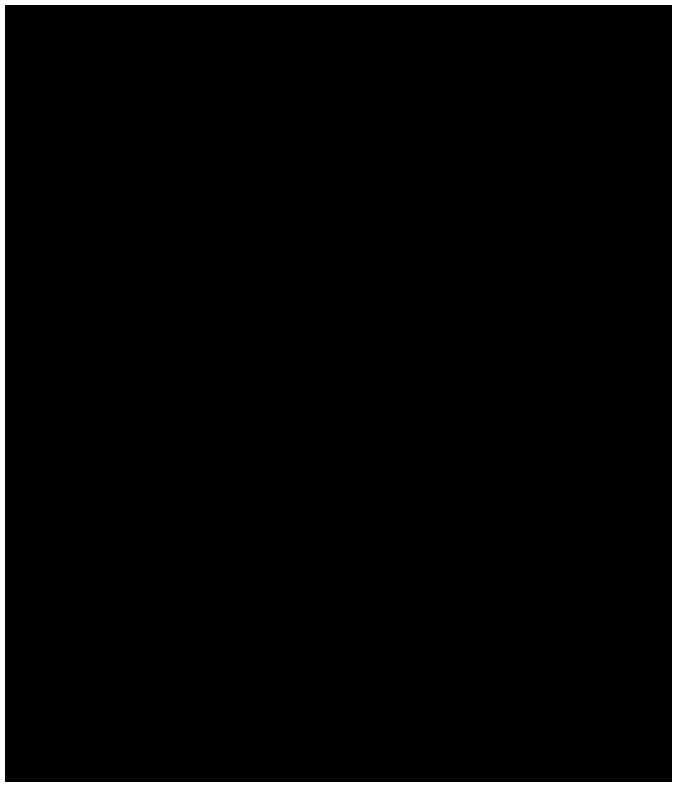
Osteopenia

Osteopenia is a condition that is common to all metabolic bone diseases. It is characterized by a reduction in bone mass greater than expected for age, race, or sex, and it occurs because of a decrease in bone formation, inadequate bone mineralization, or excessive bone deossification. *Osteopenia* is not

KEY CONCEPTS

METABOLIC BONE DISORDERS

- Metabolic bone disorders have their origin in the bone remodeling process that involves an orderly sequence of osteoclastic bone reabsorption, the formation of new bone by the osteoblasts, and mineralization of the newly formed osteoid tissue.
- Osteoporosis represents an increased loss of total bone mass due to an imbalance between bone absorption and bone formation, most often related to the aging process and decreased estrogen levels in postmenopausal women.
- Osteomalacia and rickets represent a softening of bone due to inadequate mineralization of the bone matrix caused by a deficiency of calcium or phosphate.
- Paget's disease is a disorder involving excessive bone destruction and repair, resulting in structural deformities of long bones, spine, pelvis, and cranium.



a diagnosis but a term used to describe an apparent lack of bone seen on x-ray studies. The major causes of osteopenia are osteoporosis, osteomalacia, malignancies such as multiple myeloma, and endocrine disorders such as hyperparathyroidism and hyperthyroidism.

Osteoporosis

Osteoporosis is skeletal disorder characterized by the loss of bone mass and deterioration of the architecture of cancellous bone with a subsequent increase in bone fragility and susceptibility to fractures.[3] Osteoporosis can be classified as primary or secondary. Primary osteoporosis occurs in postmenopausal women and in elderly persons of both sexes. Secondary osteoporosis is associated with a definite cause, including a variety of endocrine disorders and genetic abnormalities.

Primary osteoporosis is extremely common in the United States. Ten million Americans already have osteoarthritis, and another 34 million have low bone mass placing them at risk for the disease. Osteoporosis is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures and approximately 700,000 vertebral fractures.[3]

Pathogenesis

Regardless of cause, osteoporosis reflects enhanced bone resorption relative to bone formation. Although both of these factors play a role in most cases of osteoporosis, their relative contribution to bone loss may vary dependent upon age, sex, nutritional status, and genetic predisposition.

Under normal conditions, bone mass increases steadily during childhood, reaching a peak in the young adult years. The peak bone mass is an important determinant of the subsequent risk of osteoporosis. It is determined in part by genetic factors, gonadal (estrogen) levels, exercise, calcium intake and absorption, and environmental factors. Genetic factors are linked, in largest part, to the maximal amount of bone in a given person, referred to as *peak bone mass*. Bone mass positively correlates with the amount of skin pigmentation; whites have the least bone mass, and African Americans have the most. Mexican-American women have bone mass intermediate between non-Hispanic white women and African American women. Although osteoporosis is uncommon among African-American women, many cases are seen among postmenopausal women with brown and yellow skin.[4] Exercise may prevent osteoporosis by increasing peak bone mineral density during periods of growth. Poor nutrition or an age-related decrease in intestinal absorption of calcium because of deficient activation of vitamin D may contribute to the development of osteoporosis, particularly in the elderly.

Hormonal factors play a significant role in the development of osteoporosis, particularly in postmenopausal women. Postmenopausal osteoporosis, which is caused by an estrogen deficiency, is manifested by a loss of cancellous bone and a predisposition to fractures of the vertebrae and distal radius. The loss of bone mass is greatest during early menopause, when estrogen levels are withdrawing. Several factors appear to influence the increased loss of bone mass associated with an estrogen deficiency. Decreased estrogen levels are associated with an increase in cytokines (*e.g.*, interleukins-1, interleukin-6, and tumor necrosis factor [TNF]) that stimulate the production of osteoclast precursors. Recent studies indicate that estrogen deficiency also influences osteoclast differentiation via the RANK receptor pathways.[2] Estrogen stimulates the production of OPG and thus inhibits the formation of osteoclasts, and it also blunts the responsiveness of osteoclast precursors to the RANK ligand. With menopause and its accompanying estrogen deficiency, this inhibition of osteoclast production is lost.[2] Evidence also suggests that estrogen deficiency, as well as normal aging, may lead to decreased osteoblastic activity and new bone formation. Thus, the bone loss associated with estrogen deficiency may be caused by a combination of increased bone resorption and decreased bone formation. Testosterone deficiency may contribute to bone loss in men with senile osteoporosis, although the effect is not of the same magnitude as that caused by estrogen deficiency.

Age-related changes in bone density occur in all individuals and contribute to the development of osteoporosis in both sexes. After maximal bone mass is attained at about 30 years of age, the rate of bone loss for both sexes is approximately 0.7% per year, and it increases to approximately 1% per year or more in menopausal women.[2] The age-related loss of bone reflects decreased osteoblast activity as well as an increase in osteoclastic activity. The greatest losses occur in areas containing abundant cancellous bone, such as the spine and femoral neck. Thus, these are common sites for fractures in persons with osteoporosis.

Secondary osteoporosis is associated with many conditions, including endocrine disorders, malabsorption disorders, malignancies, alcoholism, and certain medications. Persons with endocrine disorders such as hyperthyroidism, hyperparathyroidism, Cushing's syndrome, or diabetes mellitus are at high risk for the development of osteoporosis. Hyperthyroidism causes an acceleration of bone turnover. Some malignancies (*e.g.*, multiple myeloma) secrete osteoclast-activating factor, causing significant bone loss. Alcohol is a direct inhibitor of osteoblasts and may also inhibit calcium absorption. Glucocorticoid use is the common form of drug-related osteoporosis, and its long-term use in treatment of disorders such as rheumatoid arthritis and chronic obstructive lung disease is associated with a high rate of fractures.[3] The prolonged use of medications that increase calcium excretion, such as aluminum-containing antacids, corticosteroids, and anticonvulsants, also is associated with bone loss.[5] Persons with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) who are being treated with antiretroviral therapy may have a lower bone density and signs of osteoporosis and osteopenia.[6]

Several groups of children and adolescents are at increased risk of decreased bone mass, including premature and low–birth-weight infants who have lower than expected bone mass in the early weeks of life; children who require treatment with corticosteroid drugs (*e.g.*, those with childhood inflammatory diseases and transplant recipients); children with cystic fibrosis; and those with hypogonadal states (*e.g.*, anorexia nervosa and the female athlete triad).[2] Children with cystic fibrosis often have impaired gastrointestinal function that reduces the absorption of calcium and other nutrients, and many also require the frequent use of corticosteroid drugs.

Premature osteoporosis is being seen increasingly in female athletes because of an increased prevalence of eating disorders and amenorrhea.[7] The *female athlete triad* refers to a pattern of disordered eating that leads to amenorrhea and eventually os-

teoporosis. Poor nutrition, combined with intense training, can lead to an energy deficit that causes a lack of estrogen production by the ovary and secondary amenorrhea.[8] The lack of estrogen combined with the lack of calcium and vitamin D from dietary deficiencies results in a loss of bone density and increased risk of fractures.[8] There is a concern that athletes with low bone mineral density will be at increased risk for fractures during their competitive years. It is unclear if osteoporosis induced by amenorrhea is reversible. It most frequently affects women engaged in endurance sports, such as running and swimming; in activities where appearance is important, such as figure skating, diving, and gymnastics; or sports with weight categories, such as horse racing, martial arts, and rowing.[9]

Clinical Manifestations

Osteoporotic changes occur in the diaphysis and metaphysis of bone. The diameter of the bone enlarges with age, causing the outer supporting cortex to become thinner. In severe osteoporosis, the bones begin to resemble the fragile structure of a fine porcelain vase. There is loss of trabeculae from cancellous bone and thinning of the cortex to such an extent that minimal stress causes fractures (Fig. 43-3).

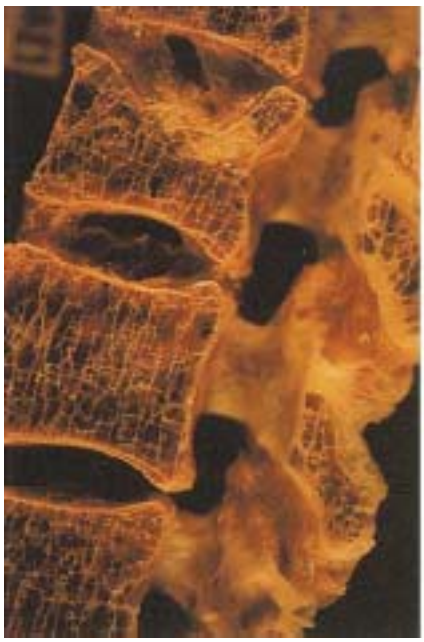
The first clinical manifestations of osteoporosis are pain accompanied by skeletal fractures—a vertebral compression fracture or fractures of the hip, pelvis, humerus, or any other bone. Fractures usually represent an end stage of the disease. Fracture occurs with a force less than typically is needed. Women who present with fractures are much more likely to sustain another fracture than are women of the same age without osteoporosis. Wedging and collapse of vertebrae causes a loss of height in the vertebral column and kyphosis, a condition commonly referred to as *dowager's hump*. Usually, there is no generalized bone tenderness. When pain occurs, it is related to fractures. Systemic symptoms such as weakness and weight loss suggest that the osteoporosis may be caused by underlying disease.

Diagnosis and Treatment

An important advance in diagnostic methods used for the identification of osteoporosis has been the use of bone mass density (BMD) studies. Several different techniques have been developed to measure BMD in multiple skeletal sites, including the vertebral column, hip, and spine. Excessive loss of height indicates some probability of low bone mass.[10] Measurement of serial heights in older adults is another simple way to screen for osteoporosis. A further advance in the diagnosis of osteoporosis is the refinement of risk factors, permitting better analysis of risk pertaining to particular persons.

Prevention and early detection of osteoporosis are essential to the prevention of the associated deformities and fractures. It is important to identify persons in high-risk groups so treatment can begin early. Postmenopausal women of small stature or lean body mass, those with sedentary lifestyles, those with poor calcium intake, and those with diseases that demineralize bone are at greatest risk. Other risk factors include an age of 80 years or greater, maternal history of hip fracture, consumption of caffeine-containing beverages, previous hyperthyroidism, and current anticonvulsant therapy. Excessive intake of diet soda that is high in phosphate also can deplete calcium stores. Other risk factors found to be associated with osteoporosis are a diet high in protein, cigarette smoking, and alcohol ingestion. Risk factors for osteoporosis are listed in Chart 43-1.

Regular exercise and adequate calcium intake are important factors in preventing osteoporosis. Weight-bearing exercises



■ **FIGURE 43-3** ■ Osteoporosis. A section of the vertebral column, in which the bone marrow has been washed out, demonstrates a loss of bone tissue and a compression fracture of a vertebral body *(top)*. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1367]. Philadelphia: Lippincott Williams & Wilkins)

CHART 43-1 Risk Factors Associated With Osteoporosis

Primary

Advanced Age
Female
White (fair, thin skin)
Small bone structure
Postmenopausal
Family History
Contributing factors
- Sedentary lifestyle
- Calcium deficiency (long-term)

Secondary

Cushing's disease
Diabetes
Hyperparathyroidism
Hyperthyroidism
Malignancy
Malabsorption disorders
Chronic alcoholism
Medications
- Anticonvulsants
- Aluminum-containing antacids
- Corticosteroids
- Heparin

such as walking, jogging, rowing, and weight lifting are important in the maintenance of bone mass. Studies have indicated that premenopausal women need more than 1000 mg and postmenopausal women need 1500 mg of calcium daily.[11] This means that adults should drink three to four glasses of milk daily or substitute other foods that are high in calcium. Because most older American women do not consume a sufficient quantity of dairy products to meet their calcium needs, calcium supplementation is recommended. Deficient activation of vitamin D may be an important factor in the impaired intestinal absorption of calcium in the elderly. A daily intake of 400 to 800 IU of vitamin D is recommended because vitamin D optimizes calcium absorption and inhibits parathyroid secretion, which stimulates calcium resorption from bone.[10]

Active treatment of osteoporosis uses four types of agents: gonadal hormones (estrogen), calcitonin, and bisphosphonates. The development of selective estrogen receptor modulators (SERMs) has been an important advance in osteoporosis research. These agents maximize the beneficial effects of estrogen on bone, while minimizing the effects on breast and endometrial tissues.[2] Calcitonin can be used to decrease osteoclastic activity and has some effect on bone pain. The bisphosphonates are analogs of endogenous inorganic pyrophosphate that the body cannot break down. In bone, they bind to hydroxyapatite and prevent bone resorption through the inhibition of osteoclast activity.

Osteomalacia and Rickets

In contrast to osteoporosis, which causes a loss of total bone mass and results in brittle bones, osteomalacia and rickets produce a softening of the bones and do not involve the loss of bone matrix.

Osteomalacia

Osteomalacia is a generalized bone condition in which inadequate mineralization of bone results from a calcium or phosphate deficiency, or both. It is sometimes referred to as the adult form of rickets.

There are two main causes of osteomalacia: (1) insufficient calcium absorption from the intestine because of a lack of dietary calcium or deficiency or resistance to the action of vitamin D and (2) phosphate deficiency caused by increased renal losses or decreased intestinal absorption. Vitamin D deficiency is caused most commonly by reduced vitamin D absorption as a result of biliary tract or intestinal diseases that impair fat and fat-soluble vitamin absorption. Lack of vitamin D in the diet is rare in the United States because many foods are fortified with the vitamin. Anticonvulsant medications, such as phenobarbital and phenytoin, induce hepatic hydroxylases that accelerate breakdown of the active forms of vitamin D.

A form of osteomalacia called *renal rickets* occurs in persons with chronic renal failure. It is caused by the inability of the kidney to activate vitamin D and excrete phosphate and is accompanied by hyperparathyroidism, increased bone turnover, and increased bone resorption (see Chapter 24). Another form of osteomalacia results from renal tubular defects that cause excessive phosphate losses. This form of osteomalacia is commonly referred to as *vitamin D-resistant rickets* and often is a familial disorder.[12] It is inherited as an X-linked dominant gene passed by mothers to one half of their children and by fathers to their daughters only. This form of osteomalacia affects boys more severely than girls. Long-standing primary hyperparathyroidism causes increased calcium resorption from bone and hypophosphatemia, which can lead to rickets in children and osteomalacia in adults.

The incidence of osteomalacia is high among the elderly because of diets deficient in calcium and vitamin D and often is compounded by the intestinal malabsorption problems that accompany aging. Osteomalacia often is seen in cultures in which the diet is deficient in vitamin D, such as in northern China, Japan, and northern India. Women in these areas have a higher incidence of the disorder than do men because of the combined effects of pregnancy, lactation, and more indoor confinement. Osteomalacia occasionally is seen in strict vegetarians, persons who have had a gastrectomy, and those on long-term anticonvulsant, tranquilizer, sedative, muscle relaxant, or diuretic drugs. There also is a greater incidence of osteomalacia in the colder regions of the world, particularly during the winter months, probably because of lessened exposure to sunlight.

The clinical manifestations of osteomalacia are bone pain, tenderness, and fractures as the disease progresses. In severe cases, muscle weakness often is an early sign. The cause of muscle weakness is unclear. The combined effects of gravity, muscle weakness, and bone softening contribute to the development of deformities. There may be a dorsal kyphosis in the spine, rib deformities, a heart-shaped pelvis, and marked bowing of the tibiae and femurs. Osteomalacia predisposes a person to pathologic fractures in the weakened areas, especially in the distal radius and proximal femur. In contrast to osteoporosis, it is not a significant cause of hip fractures. There may be delayed healing and poor retention of internal fixation devices. Osteomalacia usually is accompanied by a compensatory or secondary hyperparathyroidism stimulated by low serum calcium levels.

Diagnostic methods include x-ray studies and laboratory tests such as serum calcium, phosphate, PTH, and vitamin D levels. Bone density studies help to confirm the diagnosis. A bone biopsy may be done to confirm the diagnosis of osteomalacia.

The treatment of osteomalacia is directed at the underlying cause. If the problem is nutritional, restoring adequate amounts of calcium and vitamin D to the diet may be sufficient. Vitamin D is specific for adult osteomalacia and vitamin D-resistant rickets, but large doses usually are needed to overcome the resistance to its calcium-absorption action and to prevent renal loss of phosphate. If osteomalacia is caused by malabsorption, the treatment is directed toward correcting the primary disease. For example, adequate replacement of pancreatic enzymes is of paramount importance in pancreatic insufficiency. In renal tubular disorders, the treatment is directed at the altered renal physiology.

Rickets

Rickets is a disorder of vitamin D deficiency, inadequate calcium absorption, and impaired mineralization of bone in children. Children with rickets manifest inadequate mineralization not only of bone, but also of the cartilaginous matrix of the epiphyseal growth plate. Rickets occurs primarily in un-

derdeveloped areas of the world and among immigrants to developed countries. The causes are inadequate exposure to sunlight (*e.g.*, children are often kept clothed and indoors) and prolonged breast-feeding without vitamin D supplementation.[13] Although the vitamin D content of human milk is low, the combination of breast milk and sunlight exposure usually provides sufficient vitamin D. Another cause of rickets is the use of commercial alternative milks (*e.g.*, soy or rice beverages) that are not fortified with vitamin D.[14] A dietary deficiency in calcium and phosphorous may also contribute to the development of rickets. A newly discovered genetic mutation also can cause vitamin D deficiency rickets, a condition that does not respond to simple vitamin supplementation. The mutation results in the absence of a critical enzyme in vitamin D metabolism.[15]

The pathology of rickets is the same as that of osteomalacia seen in adults. Because rickets affects children during periods of active growth, the structural changes seen in the bone are somewhat different. Bones become deformed; ossification at epiphyseal plates is delayed and disordered, resulting in widening of the epiphyseal cartilage plate. Any new bone that does grow is unmineralized.

The symptoms of rickets usually are noticed between 6 months and 3 years of age. The child usually has stunted growth, with a height sometimes far below the normal range. Weight often is not affected so that the children, many of whom present with a protruding abdomen (*i.e.*, rachitic potbelly), have been described as presenting a Buddha-like appearance when sitting. Early symptoms are lethargy and muscle weakness, which may be accompanied by convulsions or tetany related to hypocalcemia. Irritability is common. In severe cases, children lose their skin pigment, acquire flabby subcutaneous tissue, and have poorly developed musculature. The ends of long bones and ribs are enlarged. The thorax may be abnormally shaped, with prominent rib cartilage (*i.e.*, rachitic rosary). The legs exhibit bowlegged or knock-kneed deformities. The skull is enlarged and soft, and closure of the fontanels is delayed. Teeth are slow to develop, and the child may have difficulty standing.

Rickets is treated with a balanced diet sufficient in calcium, phosphorus, and vitamin D. Exposure to sunlight also is important, especially for premature infants and those receiving artificial milk feedings. Supplemental vitamin D in excess of normal requirements is given for several months. Maintenance of good posture, positioning, and bracing in older children are used to prevent deformities. After the disease is controlled, deformities may have to be surgically corrected as the child grows.

Paget's Disease

Paget's disease (*i.e.*, osteitis deformans) is not a true metabolic disease. It is a progressive skeletal disorder that involves excessive bone destruction and repair and is characterized by increasing structural changes of the long bones, spine, pelvis, and cranium. The disease usually begins during midadulthood and becomes progressively more common thereafter.[2]

The cause of Paget's disease is unknown. It may be caused by a virus capable of inciting osteoclastic activity.[2,12] It has been suggested that the virus may induce secretion of interferon-6, which is a potent stimulator of osteoclastic recruitment and resorptive activity.[2] The disease usually begins insidiously and progresses slowly over many years. An initial osteolytic phase is followed by an osteoblastic sclerotic phase. During the initial osteolytic phase, abnormal osteoclasts proliferate. Bone resorption occurs so rapidly that new bone formation cannot keep up, and the bone is replaced by fibrous tissue. The two processes of destruction and rebuilding occur simultaneously. The bones increase in size and thickness because of accelerated bone resorption followed by abnormal regeneration. Irregular bone formation results in sclerotic and osteoblastic lesions. The result is a thick layer of coarse, thick bundles of trabecular bone with a rough and pitted outer surface that has the appearance of pumice (Fig. 43-4).

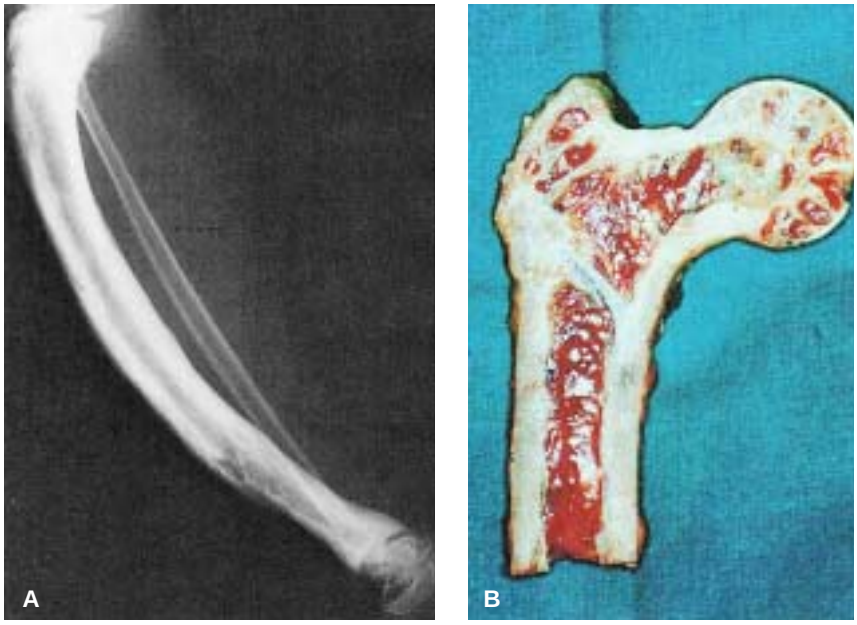
The clinical manifestations of Paget's disease depend on the specific area involved. Approximately 20% of persons with the disorder are totally asymptomatic, and the disease is discovered incidentally.[16] Involvement of the skull causes headaches, intermittent tinnitus, vertigo, and eventual hearing loss. In the spine, collapse of the anterior vertebrae causes kyphosis of the thoracic spine. The femur and tibia become bowed (Fig. 43-4). Softening of the femoral neck can cause coxa vara (*i.e.*, reduced angle of the femoral neck). Coxa vara, in combination with softening of the sacral and iliac bones, causes a waddling gait. When the lesion affects only one bone, it may cause only mild pain and stiffness. Progressive deossification weakens and distorts the bone structure. The deossification process begins along the inner cortical surfaces and continues until the substance of the bone disappears. Pathologic fractures may occur, especially in the bones subjected to the greatest stress (*e.g.*, upper femur, lower spine, pelvic bones). These fractures often heal poorly, with excessive and poorly distributed callus.

Other manifestations of Paget's disease include nerve palsy syndromes from lesions in the upper extremities, mental deterioration, and cardiovascular disease. Cardiovascular disease is the most serious complication and is listed as the most common cause of death in those with advanced generalized Paget's disease. It is caused by vasodilation of the vessels in the skin and subcutaneous tissues overlying the affected bones. When one third to one half of the skeleton is affected, the increased blood flow may lead to high-output cardiac failure. Ventilatory capacity may be limited by rib and spine involvement.

Osteogenic sarcomas occur in 5% to 10% of persons with severe disease.[2] One fifth of all osteogenic sarcomas in persons 50 years of age or older originate in people with Paget's disease.[17] The bones most often affected, in order of frequency, are the femur, pelvis, humerus, and tibia.

Diagnosis of Paget's disease is based on characteristic bone deformities and x-ray changes. Elevated levels of serum alkaline phosphatase and urinary hydroxyproline support the diagnosis, and continued surveillance of these levels may be used to monitor the effectiveness of treatment. Technetium pyrophosphate bone scans are used to detect the rapid bone turnover indicative of active disease and to monitor the response to treatment. The scan cannot identify bone activity resulting from malignant lesions. Bone biopsy may be done to differentiate the lesion from osteomyelitis or a primary or metastatic bone tumor.

The treatment of Paget's disease is based on the degree of pain and the extent of the disease. Pain can be reduced with nonsteroidal or other anti-inflammatory agents. Suppressive agents such as the hormone calcitonin, mithramycin, and



■ **FIGURE 43-4** ■ Paget disease. (**A**) Radiograph of the leg shows marked involvement of the tibia by Paget disease with thickening and disorganization of the cortex. Note the normal appearance of the fibula. (**B**) The proximal end of a femur affected by Paget disease shows replacement of the normal cancellous architecture by coarse, thick bundles of trabecular bone. The cortical bone is irregularly thickened and exhibits a coarse, granular appearance instead of the normally smooth cortical bone. Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1377]. Philadelphia: Lippincott Williams & Wilkins)

bisphosphonates are used to manage pain and prevent further spread of the disease and neurologic defects. Calcitonin, administered by nasal spray, inhibits osteoclast-mediated bone resorption. Bisphosphonates are the treatment of choice for Paget's disease. They act by binding directly to bone minerals, inhibiting bone loss by rapidly decreasing bone resorption, followed by a secondary slower decrease in the rate of bone formation.

In summary, in addition to its structural function, the skeleton is a homeostatic organ. Metabolic bone diseases such as osteoporosis, osteomalacia, rickets, and Paget's disease are the result of a disruption in the equilibrium of bone formation and resorption. Osteoporosis, which is the most common of the metabolic bone diseases, occurs when the rate of bone resorption is greater than that of bone formation. It is seen frequently in postmenopausal women and is the major cause of fractures in persons older than 45 years of age. Osteomalacia and rickets are caused by inadequate mineralization of bone matrix, primarily because of a deficiency of vitamin D. Paget's disease results from excessive osteoclastic activity and is characterized by the formation of poor-quality bone.

RHEUMATIC DISORDERS

Rheumatic disorders are characterized by inflammation, pain, and stiffness in the musculoskeletal system. *Arthritis* is a descriptive term applied to more than 100 rheumatic diseases, ranging from localized, self-limiting conditions to those that are systemic, autoimmune processes.[18,19] Arthritis affects persons in all age groups and is the leading cause of disability in the United States.

The common use of the term *arthritis* oversimplifies the nature of the varied disease processes, the difficulty in differentiating one form of arthritis from another, and the complexity of treatment of these usually chronic conditions. These diverse rheumatic conditions share inflammation of the joint as a prominent or accompanying symptom. In the systemic rheumatic diseases, such as rheumatoid arthritis, the inflammation is primary, resulting from an immune response, probably autoimmune in origin. In rheumatic conditions limited to a single or few diarthrodial joints, such as osteoarthritis, the inflammation is secondary, resulting from the degenerative process and joint irregularities.

Systemic Autoimmune Rheumatic Diseases

Systemic autoimmune rheumatic diseases are a group of chronic disorders characterized by diffuse inflammatory vascular lesions and degenerative changes in connective tissue that share clinical features and may affect many of the same organs. They

KEY CONCEPTS

ARTHRITIS

- Arthritis represents a diverse group of rheumatic conditions that share inflammation of the joint as a prominent or accompanying symptom.
- In the systemic rheumatic diseases, the inflammation is primary, resulting from an immune response, probably autoimmune in origin.
- In rheumatic conditions, such as osteoarthritis, which are limited to a single or few diarthrodial joints, the inflammation is secondary, resulting from the degenerative process and joint irregularities.

include rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis, all of which share an autoimmune systemic pathogenesis.

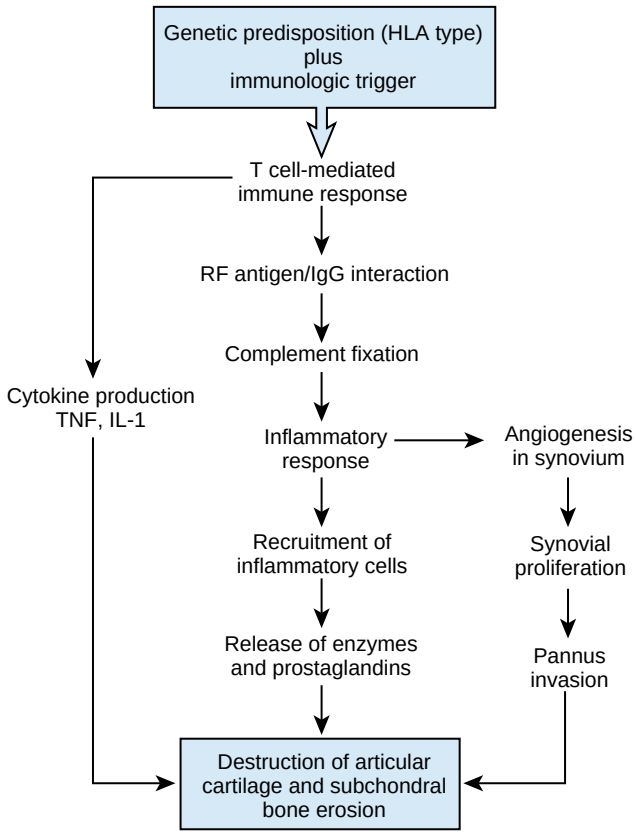
Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects 0.3% to 1.5% of the population, with women affected two to three times more frequently than men.[18] Although the disease occurs in all age groups, its prevalence increases with age. The peak incidence among women is between the ages of 40 and 60 years, with the onset at 30 to 50 years of age.

Although the cause of RA remains uncertain, evidence points to a genetic predisposition and the development of joint inflammation that is immunologically mediated. It has been suggested that the disease is initiated in a genetically predisposed individual by the activation of a T cell-mediated response to an immunologic trigger, such as a microbial agent. The importance of genetic factors in the pathogenesis of RA is supported by the increased frequency of the disease among first-degree relatives and monozygotic twins. There is also a strong association of human leukocyte antigen (HLA) DR4 and/or HLA-DRB1 with RA.[18] Thus, certain HLA-DR molecules may predispose to RA by their capacity to bind arthrogenic antigens, which in turn activate helper T cells and initiate the disease.

Pathogenesis. The pathogenesis of RA can be viewed as an aberrant immune response that leads to synovial inflammation and destruction of the joint architecture. Approximately 85% of those with the disease have a substance called the *rheumatoid factor* (RF), which is an autoantibody that reacts with a fragment of immunoglobulin G (IgG).[12,20] The RF and IgG form immune complexes that fix complement; attract neutrophils, macrophages, and lymphocytes; and incite the inflammatory response (Fig. 43-5). The presence of high titers of RF is frequently associated with severe and unremitting disease, many systemic complications, and a serious prognosis.[12] However, it is important to note that about 15% persons with RA do not have the RF, and the factor is occasionally found in other disease states (and even healthy people).

Characteristic of RA is the development of an extensive network of new blood vessels in the synovial membrane that contributes to the advancement of the rheumatoid synovitis. This destructive vascular granulation tissue, which is called *pannus*, extends from the synovium to involve the "bare area," a region of unprotected bone at the junction between cartilage and subchondral bone. Pannus is a feature of RA that differentiates it from other forms of inflammatory arthritis[21] (Fig. 43-6). The inflammatory cells found in the pannus have a destructive effect on the adjacent cartilage and bone. Eventually, pannus develops between the joint margins, leading to reduced joint motion and the possibility of eventual ankylosis. With progression of the disease, joint inflammation and the resulting structural changes can lead to joint instability, muscle atrophy from disuse, stretching of the ligaments, and involvement of the tendons and muscles. The effect of the pathologic changes on joint structure and function is related to the degree of disease activity, which can change at any time. Unfortunately, the destructive changes are irreversible.



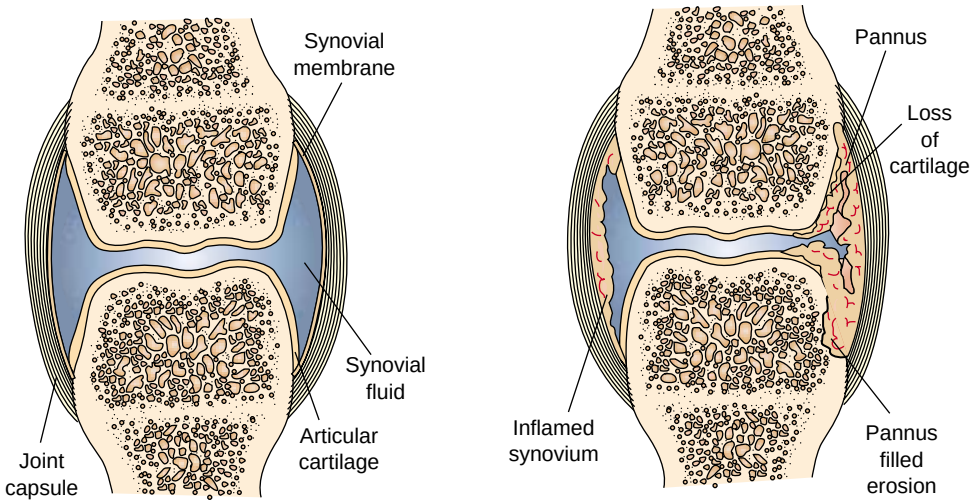
■ **FIGURE 43-5** ■ Disease process in rheumatoid arthritis.

Clinical Manifestations. Rheumatoid arthritis often is associated with systemic as well as joint manifestations. It usually has an insidious onset marked by systemic manifestations such as fatigue, anorexia, weight loss, and low-grade fever when the disease is active. The erythrocyte sedimentation rate (ESR), which commonly is elevated during inflammatory processes, has been found to correlate with the amount of disease activity.[22] Anemia associated with a low serum iron level or low iron-binding capacity is common.[18] This anemia usually is resistant to iron therapy.

The disease, which is characterized by exacerbations and remissions, may involve only a few joints for brief durations, or it may be relentlessly progressive and debilitating. Approximately 3% of those with the disease have a progressive, unremitting form that does not respond to aggressive therapy.[18]

Joint Manifestations. Joint involvement usually is symmetric and polyarticular. Any diarthrodial joint can be involved. The person may report joint pain and stiffness that lasts 30 minutes and frequently for several hours. The limitation of joint motion that occurs early in the disease usually is caused by pain; later, it is caused by fibrosis. The most frequently affected joints initially are the fingers, hands, wrists, knees, and feet. Later, other diarthrodial joints may become involved. Spinal involvement usually is limited to the cervical region.

In the hands, there usually is bilateral and symmetric involvement of the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints in the early stages of RA; the distal interphalangeal (DIP) joints rarely are affected. The fingers



■ **FIGURE 43-6** ■ (**Left**) Normal joint structures. (**Right**) Joint changes in rheumatoid arthritis. The left side denotes early changes occurring within the synovium, and the right side shows progressive disease that leads to erosion and the formation of pannus.

often take on a spindle-shaped appearance because of inflammation of the PIP joints (Fig. 43-7). Progressive joint destruction may lead to subluxation (*i.e.*, dislocation of the joint resulting in misalignment of the bone ends) and instability of the joint and in limitation of movement. Swelling and thickening of the synovium can result in stretching of the joint capsule and ligaments. When this occurs, muscle and tendon imbalances develop, and mechanical forces applied to the joints through daily activities produce joint deformities. In the MCP joints, the extensor tendons can slip to the ulnar side of the metacarpal head, causing ulnar deviation of the finger (Fig. 43-8). Subluxation of the MCP joints may develop when this deformity is present. Hyperextension of the PIP joint and partial flexion of the DIP joint is called a *swan neck deformity*. After this condition becomes fixed, severe loss of function occurs because the person can no longer make a fist. Flexion of the PIP joint with hyperextension of the DIP joint is called a *boutonnière deformity*.

The knee is one of the most commonly affected joints and is responsible for much of the disability associated with the disease.[18] Active synovitis may be apparent as visible swelling that obliterates the normal contour over the medial and lateral aspects of the patella. The *bulge sign*, which involves milking fluid from the lateral to the medial side of the patella, may be used to determine the presence of excess fluid when it is not visible. Joint contractures, instability, and genu valgus (knock-knee) deformity are other possible manifestations. Severe quadriceps atrophy can contribute to the disability. *Baker's cyst* may occur in the popliteal area behind the knee. This is caused by enlargement of the bursa and usually does not cause symptoms unless the cyst ruptures, in which case symptoms mimicking thrombophlebitis appear.

Because the lower extremity joints are weight-bearing structures, involvement of the foot and ankle causes greater dysfunction and pain than does involvement of the upper extrem-

ities. Disease activity can limit flexion and extension of the ankle, which can create difficulty in walking. Involvement of the metatarsophalangeal joints of the feet can cause subluxation, hallux valgus, and hammer toe deformities.

Neck discomfort is common. In rare cases, long-standing disease can lead to neurologic complications such as occipital headaches, muscle weakness, and numbness and tingling in the upper extremities. More severe but less common neurologic complications are dislocation of the first cervical vertebra and subluxation of the odontoid process of the second vertebra into the foramen magnum, which can lead to paralysis and is potentially fatal.

Extra-articular Manifestations. Although characteristically a joint disease, RA can affect a number of other tissues. Extra-articular manifestations probably occur with a fair degree of frequency but usually are mild enough to cause few problems. They are most likely to occur in persons with the RF.

Rheumatoid nodules are granulomatous lesions that develop around small blood vessels. The nodules may be tender or nontender, movable or immovable, and small or large. Typically, they are found over pressure points such as the extensor surfaces of the ulna. The nodules may remain unless surgically removed, or they may resolve spontaneously.

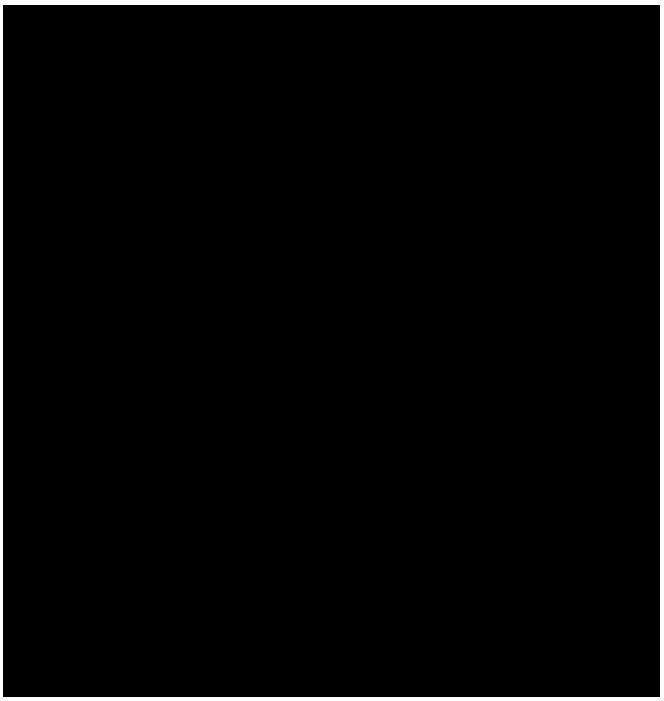
Vasculitis, involving the small and medium-size arterioles, is an uncommon manifestation of RA in persons with a long history of active arthritis and high titers of RF (see Chapter 15). Manifestations include ischemic areas in the nail fold and digital pulp that appear as brown spots. Ulcerations may occur in the lower extremities, particularly around the malleolar areas. In some cases, neuropathy may be the only symptom of vasculitis. The visceral organs, such as the heart, lungs, and gastrointestinal tract, also may be affected.

Other extra-articular manifestations include eye lesions such as episcleritis and scleritis, hematologic abnormalities, pulmonary disease, cardiac complications, infection, and Felty's syndrome (*i.e.*, leukopenia with or without splenomegaly).

Diagnosis and Treatment. The diagnosis of RA is based on findings of the history, physical examination, and laboratory tests. The criteria for RA developed by the American Rheumatism Association are useful in establishing the diagnosis[23] (Chart 43-2). At least four of the criteria must be present to make a diagnosis of RA. Although these criteria were developed for classification purposes and for use in epidemiological studies, they can be used as guidelines for diagnosing the illness in individual patients.

In the early stages, the disease often is difficult to diagnose. On physical examination, the affected joints show signs of inflammation, swelling, tenderness, and possibly warmth and reduced motion. The joints have a soft, spongy feeling because of the synovial thickening and inflammation. Body movements may be guarded to prevent pain. Changes in joint structure usually are not visible early in the disease.

The RF test results are not diagnostic for RA, but they can be of value in differentiating RA from other forms of arthritis. Radiologic findings also are not diagnostic in RA because joint erosions often are not seen on radiographic images in the early stages of the disorder. Synovial fluid analysis can be helpful in the diagnostic process. The synovial fluid has a cloudy appearance, the white blood cell count is elevated as a result of inflammation, and the complement components are decreased.



The treatment plan for a person with RA includes education about the disease and its treatment, rest, therapeutic exercises, and medications. Because of the chronicity of the disease and the need for continuous, long-term adherence to the prescribed treatment modalities, it is important that the treatment be integrated into the person's lifestyle.

The goals of pharmacologic therapy for RA are to reduce pain, decrease inflammation, maintain or restore joint function, and prevent bone and cartilage destruction. Nonsteroidal anti-inflammatory drugs (NSAIDs) usually are the first choice in the treatment of RA. The NSAIDs, including the salicylates (*e.g.*, aspirin), and the newer COX-2 inhibitors, provide anti-inflammatory and analgesic effects. Second-line drug therapy is initiated early in the disease if joint symptoms persist despite use of NSAIDs. Disease-modifying antirheumatic drugs (DMARDs) include gold salts, hydroxychloroquine, sulfasalazine, methotrexate, and azathioprine. Methotrexate, a potent immunosuppressive drug, has become the drug of choice because of its potency. It is also relatively fast acting (*i.e.*, improvement is seen in 1 month) compared with the slower-acting DMARDs, which can take 3 to 4 months to work. Corticosteroid drugs may be used to reduce discomfort.[24] To avoid long-term side effects, they are used only in specific situations for short-term therapy at a low dose level. This medication does not modify the disease and is unable to prevent joint destruction. Intra-articular corticosteroid injections can provide rapid relief of acute or subacute inflammatory synovitis in a few joints.

Newer antirheumatic drugs include leflunomide, etanercept, and infliximab. Leflunomide is a pyrimidine synthesis inhibitor that blocks the expansion of T cells.[25] Infliximab (Remicade) and etanercept (Enbrel) are biologic response-modifying agents that block tumor necrosis factor-α (TNF-α), one of the key proinflammatory cytokines in RA.

Surgery also may be a part of the treatment of RA. Synovectomy may be indicated to reduce pain and joint damage when synovitis does not respond to medical treatment. Total joint replacements (*i.e.*, arthroplasty) may be performed to reduce pain and increase motion. Arthrodesis (*i.e.*, joint fusion) is indicated only in extreme cases when there is so much soft tissue damage and scarring or infection that a replacement is impossible.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect virtually any organ system, including the skin, joints, kidneys, serosal membranes, and heart. SLE is a major rheumatic disease, and more than 90% of persons with the disease have polyarthralgias. SLE is a fairly common disease with a prevalence of approximately 1 case per 2000 persons in certain populations.[26] The peak incidence occurs between ages 15 to 40 years. There is a female-to-male ratio of 9 to 1, with the ratio becoming closer to 30 to 1 during the childbearing years. SLE is more common in African Americans, Hispanics, and Asians than whites, and the incidence in some families is higher than in others.[18]

The cause of SLE is unknown. The presence of a wide array of autoantibodies suggests a breakdown in the normal surveillance function of the immune system (see Chapter 10). Antibodies have been identified against a host of nuclear and cytoplasmic components of the cell that are neither tissue nor organ specific. Antinuclear antibodies (ANAs) are directed against several nuclear antigens, including DNA, histones, nonhistone proteins bound to RNA, and nucleolar antigens.[26] Another group of antibodies is directed against cell surface antigens of blood elements.

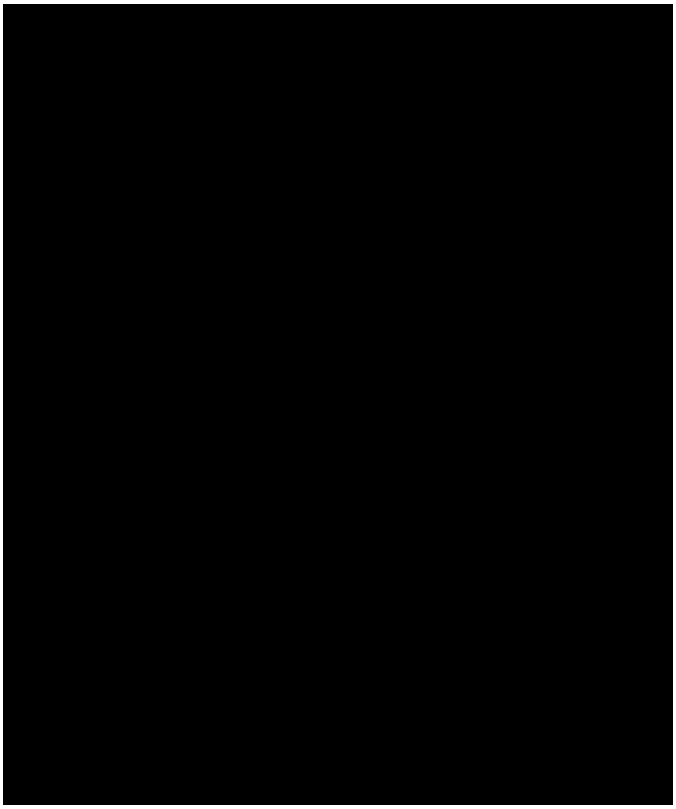
The development of autoantibodies is thought to result from a combination of factors, including genetic, hormonal, immunologic, and environmental factors. Genetic predisposition is evidenced by the occurrence of familial cases of SLE, especially among identical twins. In North American white populations there is a positive association between SLE and class II HLA genes, particularly at the HLA-DQ locus (see Chapter 9).[27] Studies also suggest that an imbalance in sex hormone levels may play a role in the development of the disease, especially because the disease is so prevalent among women. Androgens appear to protect against and estrogens seem to favor the development of SLE.[18] Possible environmental triggers include ultraviolet (UV) light, certain drugs, and possibly infectious agents. UV light, specifically UVB associated with exposure to the sun or unshielded fluorescent bulbs, may trigger exacerbations. Photosensitivity occurs in approximately one third of patients with SLE.

Pathogenesis. The pathologic process probably begins with exaggerated production of autoantibodies. The autoantibodies combine with corresponding antigens to form immune complexes. These immune complexes are deposited in vascular and tissue surfaces, triggering an inflammatory response and ultimately causing local tissue injury. Some autoantibodies that have been identified in SLE include anti-deoxyribonucleic acid (DNA). Other antibodies may be produced against various cells, including red blood cell surface antigens, platelets, and coagulation factors. Autoantibodies against red blood cells can lead to anemia and those against platelets to thrombocytopenia. Certain drugs may provoke a lupus-like disorder in susceptible persons, particularly in the elderly. The most common of these drugs are hydralazine and procainamide. Other drugs, such as quinidine, methyldopa, isoniazid, and phenytoin, also have been known to produce this syndrome. The disease usually recedes when use of the drug is discontinued.

Clinical Course. Systemic lupus erythematosus can manifest in a variety of ways. The disease has been called the *great imitator* because it has the capacity for affecting many different body systems, including the musculoskeletal system, the skin, the cardiovascular system, the lungs, the kidneys, the central nervous system (CNS), and the red blood cells and platelets. The onset may be acute or insidious, and the course of the disease is characterized by exacerbations and remissions.[27]

Arthralgias and arthritis are among the most commonly occurring early symptoms of SLE; approximately 90% of all persons with the disease report joint pain at some point during the course of their disease.[27] The polyarthritis of SLE initially can be confused with other forms of arthritis, especially RA, because of the symmetric arthropathy. Ligaments, tendons, and the joint capsule may be involved, causing varied deformities in approximately 30% of persons with the disease. Flexion contractures, hyperextension of the interphalangeal joint, and subluxation of the carpometacarpal joint contribute to the deformity and subsequent loss of function in the hands. Other musculoskeletal manifestations include tenosynovitis, rupture of the intrapatellar and Achilles tendons, and avascular necrosis, frequently of the femoral head.

Skin manifestations can vary greatly and may be classified as acute, subacute, or chronic. The acute skin lesions include the classic malar or "butterfly" rash on the nose and cheeks (Fig. 43-9). This rash is seen in SLE but may be associated with



other skin lesions, such as hives or livedo reticularis (*i.e.*, reticular cyanotic discoloration of the skin, often precipitated by cold) and fingertip lesions, such as periungual erythema, nail fold infarcts, and splinter hemorrhages. Hair loss is common. Mucous membrane lesions tend to occur during periods of exacerbation. Sun sensitivity may occur in SLE even after mild sun exposure. Discoid SLE (*i.e.*, chronic cutaneous lupus) involves plaquelike lesions on the head, scalp, and neck. These lesions first appear as red, swollen patches of skin, and later there can be scarring, depigmentation, and plugging of hair follicles. Ninety percent of patients with discoid lupus have disease that involves only the skin.

Renal involvement occurs in approximately 50% of persons with SLE. Several forms of glomerulonephritis may occur, including mesangial, focal proliferative, diffuse proliferative, and membranous (see Chapter 23). Interstitial nephritis also may occur. Nephrotic syndrome causes proteinuria with resultant edema in the legs, abdomen, and around the eyes.

The heart and lungs frequently are sites of complications in people with SLE.[27] Pulmonary involvement in SLE occurs in 40% to 50% of patients and is manifested primarily by pleural effusions or pleuritis. Less frequently occurring pulmonary problems include acute pneumonitis, pulmonary hemorrhage, chronic interstitial lung disease, and pulmonary embolism. Pericarditis, often accompanied by pleural effusions, is the most common of the cardiac manifestations of SLE. Myocarditis affects as many as 25% of those with SLE. Hypertension may be associated with lupus nephritis and long-term corticosteroid use. Ischemic heart disease can occur in older patients with longer-duration SLE. Hematologic disorders may manifest as hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia.

The CNS is involved in 30% to 75% of persons with SLE. The pathologic basis for the CNS symptoms is not entirely clear. It has been ascribed to an acute vasculitis that impedes blood flow, causing strokes or hemorrhage; an immune response involving antineuronal antibodies that attack nerve cells; or production of antiphospholipid antibodies that damage blood vessels and cause blood clots in the brain. Seizures can occur and are more common when renal failure is present. Psychotic symptoms, including depression and unnatural euphoria, as well as decreased cognitive functioning, confusion, and altered levels of consciousness, may develop.

Subacute cutaneous lupus erythematosus (SCLE) is a less severe form of lupus. The skin lesions in this condition may resemble psoriasis. These lesions are found in sun-exposed areas, such as the face, chest, upper back, and arms. Patients with SCLE may have mild systemic problems, which usually are limited to joint and muscle pains.

Diagnosis and Treatment. The diagnosis of SLE is based on a complete history, physical examination, and analysis of blood work. No single test can diagnose SLE in all persons. The most common laboratory test performed is the immunofluorescence test for ANA. Ninety-five percent of persons with untreated SLE have high ANA levels. Although the ANA test is not specific for lupus, it establishes that the differential diagnosis includes autoimmunity. The anti-DNA antibody test is more specific for the diagnosis of SLE.[27] Other serum tests may reveal moderate to severe anemia, thrombocytopenia, and leukocytosis or leukopenia. Additional immunologic tests may be done to give support to the diagnosis or to differentiate SLE from other connective tissue diseases.

Treatment of SLE focuses on managing the acute and chronic symptoms of the disease. The goals of treatment include preventing progressive loss of organ function, reducing the possibility of exacerbations, minimizing disability from the disease process, and preventing complications from medication therapy.[28] Treatment with medications may be as simple as a drug to reduce inflammation, such as an NSAID. NSAIDs can control fever, arthritis, and mild pleuritis. An antimalarial drug (*e.g.*, hydroxychloroquine) may be the next medication considered to treat cutaneous and musculoskeletal manifestations of SLE. Corticosteroids are used to treat more significant symptoms of SLE, such as renal and CNS disorders. Immunosuppressive drugs are used in cases of severe disease.

Systemic Sclerosis

Systemic sclerosis, sometimes called *scleroderma*, is an autoimmune disease of connective tissue characterized by excessive collagen deposition in the skin and internal organs, such as the lungs, gastrointestinal tract, heart, and kidneys. In this disorder, the skin is thickened through fibrosis, with an accompanying fixation of subdermal structures, including the sheaths or fascia covering tendons and muscles.[29] Systemic sclerosis affects women four times as frequently as men, with a peak incidence in the 35-year to 50-year age group.[12] The cause of this rare disorder is poorly understood. There is evidence of both humoral and cellular immune system abnormalities.

Scleroderma presents as two distinct clinical entities: the diffuse or generalized form of the disease and the limited or CREST variant. In the CREST syndrome, hardening of the skin (scleroderma) is limited to the hands and face; whereas, the skin changes in diffuse scleroderma also involve the trunk and proximal extremities. Almost all persons with scleroderma develop polyarthritis and Raynaud's phenomenon, a vascular disorder characterized by reversible vasospasm of the arteries supplying the fingers (see Chapter 15).

Diffuse scleroderma is characterized by severe and progressive disease of the skin and the early onset of organ involvement. The typical person has a "*stone facies*" caused by tightening of the facial skin with restricted motion of the mouth. Involvement of the esophagus leads to hypomotility and difficulty swallowing. Malabsorption may develop if the submucosal and muscular atrophy affect the intestine. Pulmonary involvement leads to dyspnea and eventually respiratory failure. Vascular involvement of the kidneys is responsible for malignant hypertension and progressive renal insufficiency. Cardiac problems include pericarditis, heart block, and myocardial fibrosis.

The CREST syndrome is manifest by calcinosis (*i.e.*, calcium deposits in the subcutaneous tissue that erupt through the skin), Raynaud's phenomenon, esophageal dysmotility, sclerodactyly (localized scleroderma of the fingers), and telangiectasia.[30]

Treatment of systemic sclerosis is largely symptomatic and supportive. The 9-year survival rate is about 40%.[30] Studies have indicated that if heart, lung, or kidney involvement is to become severe, it tends to do so early in disease and is a predictor of shortened survival. Patients who survive the first few years without experiencing severe organ involvement are less likely to experience life-threatening involvement later in their illness.[30]

Seronegative Spondyloarthropathies

The *spondyloarthropathies* are an interrelated group of multisystem inflammatory disorders that primarily affect the axial skeleton, particularly the spine. Because there is an absence of the RF, these disorders often are referred to as *seronegative spondyloarthropathies*. In contrast to RA, the inflammation begins at sites where tendons and ligament insert into bone, rather than in the synovium. Sacroiliitis is the pathologic hallmark. Persons with the disorder may also have inflammation and involvement of the peripheral joints, in which case the signs and symptoms overlap with other inflammatory types of arthritis. The seronegative spondyloarthropathies include ankylosing spondylitis, reactive arthritis, and psoriatic arthritis.

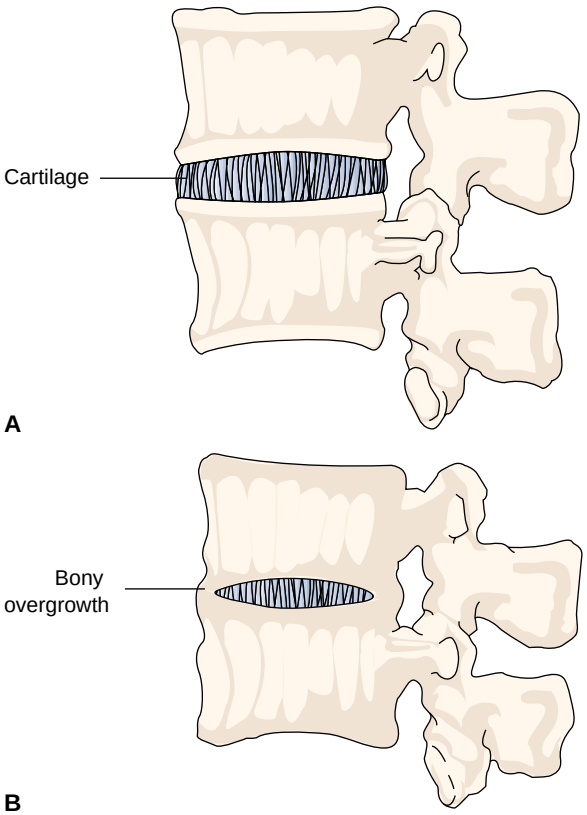
The pathogenesis of the spondyloarthropathies is unclear. However, there is a striking association with the HLA-B27 antigen. The HLA-B27 antigen is also found in the normal population; thus, it is neither necessary nor sufficient for the development of any of the diseases.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic, systemic inflammatory disease of the joints of the axial skeleton, manifested by pain and progressive stiffening of the spine. The disorder begins in the sacroiliac joints bilaterally and then smaller joints of the posterior elements of the spine. The result is the ultimate destruction of these joints with ankylosis or posterior fusion of the spine. The vertebrae take on a squared appearance, and bone bridges fuse one vertebral body to the next across the intervertebral discs (Fig. 43-10). Progressive spinal changes usually follow an ascending pattern up the spine. Occasionally, large synovial joints (*i.e.*, hips, knees, and shoulders) may be involved. The small peripheral joints usually are not affected. The disease affects approximately 2% to 8% of the HLA-B27–positive white population.[18] Clinical manifestations usually begin in late adolescence or early adulthood and are slightly more common in men than in women. The disease spectrum ranges from an asymptomatic sacroiliitis to a progressive disease that can affect many body systems.

The pathogenesis of ankylosing spondylitis remains unclear. The presence of mononuclear cells in acutely involved tissue suggests an immune response in which genetic and environmental factors play a role. The HLA-B27 antigen remains one of the best-known examples of an association between a disease and a hereditary marker. Approximately 90% of those with ankylosing spondylitis have the HLA-B27 antigen, and nearly 100% of those who also have uveitis or aortitis have the marker. Although the mechanism by which HLA-B27 influences the development of ankylosing spondylitis remains to be discovered, it has been proposed that the HLA-B27 antigen and some environmental trigger are structurally related in a manner that induces an autoimmune response.

Clinical Manifestations. The person with ankylosing spondylitis typically reports low back pain, which may be persistent or intermittent. The pain, which becomes worse when resting, particularly when lying in bed, initially may be blamed on muscle strain or spasm from physical activity. Lumbosacral pain also may be present, with discomfort in the buttocks and hip areas. Sometimes, pain can radiate to the thigh in a manner similar to that of sciatic pain. Prolonged stiffness is present in the morning and after periods of rest. Mild physical activity



■ **FIGURE 43-10** ■ The bony overgrowth (**B**) of the vertebra characteristic of ankylosing spondylitis is evident when compared with normal vertebra (**A**).

or a hot shower helps reduce pain and stiffness. Sleep patterns frequently are interrupted because of these manifestations. Walking or exercise may be needed to provide the comfort needed to return to sleep. Muscle spasm also may contribute to discomfort.

Loss of motion in the spinal column is characteristic of the disease. The severity and duration of disease activity influence the degree of mobility. Loss of lumbar lordosis occurs as the disease progresses, and this is followed by kyphosis of the thoracic spine and extension of the neck. A kyphotic spine makes it difficult for the patient to look ahead and to maintain balance while walking. The image is one of a person bent over looking at the floor and unable to straighten. X-ray films show a rigid, bamboo-like spine. The heart and lungs are constricted in the chest cavity. Abnormal weight bearing can lead to degeneration and destruction of the peripheral joints, most commonly the hips, shoulders and knees.

The most common extraskeletal involvement is acute anterior uveitis (inflammation of uvea of the eye), which occurs in 25% to 30% of patients sometime in the course of their disease.[18] Systemic features of weight loss, fever, and fatigue may be apparent. Sometimes, the fatigue is a greater problem than pain or stiffness. Osteoporosis can occur, especially in the spine, which contributes to the risk of spinal fracture. Fusion of the costovertebral joints can lead to reduced lung volume.

Diagnosis and Treatment. The diagnosis of ankylosing spondylitis is based on history, physical examination, and x-ray ex-

amination. Laboratory findings frequently include an elevated ESR. A mild normocytic normochromic anemia may be present. Because HLA-B27 is found in 8% of the normal population, it is not a specific diagnostic test for the disease. Radiologic evaluations help differentiate sacroiliitis from other diseases.

Treatment is directed at controlling pain and maintaining mobility by suppressing inflammation. Therapeutic exercises are important to assist in maintaining motion in peripheral joints and in the spine. Muscle-strengthening exercises for extensor muscle groups also are prescribed. Immobilizing joints is not recommended. NSAIDs are used to reduce inflammation, which helps to control pain and reduce muscle spasm. Most peripheral joint pain and limitations of motion occur in the hip. Total hip replacement surgery may be used to reduce pain and increase mobility.

Reactive Arthritis

Reactive arthritis refers to a form of peripheral arthritis, often accompanied by one or more extra-articular manifestations, that occurs shortly after certain infections of genitourinary or gastrointestinal systems.[18,31,32] The majority of affected persons are young men who have inherited the HLA-B27 marker. Two forms of reactive arthritis are Reiter's syndrome and enteropathic arthritis.

Reiter's Syndrome. Reiter's syndrome is considered to be a clinical manifestation of reactive arthritis that may be accompanied by extra-articular symptoms, such as uveitis, bowel inflammation, and carditis. Reiter's syndrome develops in a genetically susceptible host after an infection by bacteria, *Chlamydia trachomatis* in the genitourinary tract, or *Salmonella, Shigella, Yersinia*, or *Campylobacter* in the gastrointestinal tract.

The arthritis is usually asymmetric and frequently involves the large weight-bearing joints (*i.e.*, the knee and ankle); sacroiliitis or ankylosing spondylitis, especially after frequent recurrences. Systemic symptoms include fever and weight loss, both of which are common at the onset of the disease. Several mucocutaneous manifestations, including balanitis, oral lesions, and skin rash are common. The skin rash, which resembles pustular psoriasis, appears most commonly on the soles of feet and palms of hands but may affect any cutaneous area. The toenails and fingernails may become thickened and opaque and may crumble, resembling the changes seen in fungal infections of the nails. Aortitis, with aortic regurgitation occurs in 1% to 2% of persons, typically after longstanding active arthritis. Although most signs of the disease disappear within days or weeks, the arthritis may persist for several months or even years. Recurrences involving any of the combination of clinical manifestations are common and sometimes followed by permanent sequelae, especially in the joints.

The treatment is largely symptomatic. NSAIDs are used to treat the arthritic symptoms. Antibiotics may be of some use in treating the triggering infection.

Enteropathic Arthritis. Arthritis that is associated with an inflammatory bowel disease usually is considered an enteropathic arthritis because the intestinal disease is directly involved in the pathogenesis. Most cases of enteropathic arthritis are classified among the spondyloarthropathies. These include cases in which the arthritis is associated with inflammatory bowel disease (*i.e.*, ulcerative colitis and Crohn's disease), the reactive arthritides triggered by enterogenic bacteria, some of the undifferentiated spondyloarthropathies, Whipple's disease, and reactions after intestinal bypass surgery.[18] There is no direct relation between the activity of the bowel disease and the degree of arthritis activity.

Psoriatic Arthritis

Psoriatic arthritis occurs in approximately 5% to 7% of people with psoriasis. It is heterogenous disorder with features typical of the spondyloarthropathies in some persons, features of RA in others, and features of both diseases coexisting in yet others.[18]

The etiology of psoriasis and psoriatic arthritis is unknown. Genetic, environmental, and immunologic factors appear to influence susceptibility and expression of disease. Environmental factors including infectious agents and physical trauma may play a role in the pathogenesis of the disorder. T cell-mediated immune responses also seem to play an important role in the skin and joint manifestations of the disease. Psoriasis improves after treatment with immunosuppressant agents such as cyclosporine.

Psoriatic arthritis may present with a variety of forms, including monoarthritis, asymmetric oligoarthritis, or symmetric polyarthritis. Usually the arthritis is asymmetric with "sausage" appearance of the fingers and toes. Sacroiliac joint involvement is common, and ankylosis of the sacroiliac joints may occur.

Although the arthritis can antedate detectable skin rash, the definitive diagnosis of psoriatic arthritis cannot be made without evidence of skin or nail changes typical of psoriasis. This heterogeneous clinical presentation suggests more than one disease is associated with psoriasis, or various clinical responses to a common cause. At least 20% of those with psoriatic arthritis have an elevated serum level of uric acid. The abnormally elevated serum uric acid level is caused by the rapid skin turnover of psoriasis, the breakdown of nucleic acid, and the metabolism to uric acid. This finding may lead to a misdiagnosis of gout. Psoriatic arthritis tends to be slowly progressive but is associated with a more favorable prognosis than RA.

Basic management is similar to that for the treatment of RA. Suppression of the skin disease may be important in helping control the arthritis. Often, affected joints are surprisingly functional and only minimally symptomatic.

Osteoarthritis Syndrome

Osteoarthritis (OA), formerly called *degenerative joint disease*, is the most prevalent form of arthritis. It is second only to cardiovascular disease as the cause of chronic disability in adults.[33] The term *osteoarthritis* encompasses a heterogeneous collection of syndromes and is more of a disease process than a specific entity. It can occur as a primary idiopathic or a secondary disorder, although this distinction is not always clear. Idiopathic or primary variants of OA occur as localized or generalized (*i.e.*, more than three joints) syndromes. Secondary OA has a known underlying cause, such as congenital or acquired defects of joint structures, trauma, metabolic disorders, or inflammatory diseases (see Chart 43-3).

One third of all adults in the United States have radiographic evidence of osteoarthritis of the hand, foot, knee, or hip. Sex and age interact to influence the time of onset and, with race, the pattern of joint involvement. Men are affected more commonly at a younger age than women, but the rate of women affected exceeds that of men by middle age. Hand OA is more likely to affect white women, whereas knee OA is more

CHART 43-3 Causes of Osteoarthritis

Postinflammatory disorders
- Rheumatoid arthritis
- Septic joint

Post-traumatic disorders
- Acute fracture
- Ligament or meniscal injury
- Cumulative occupational or recreational trauma

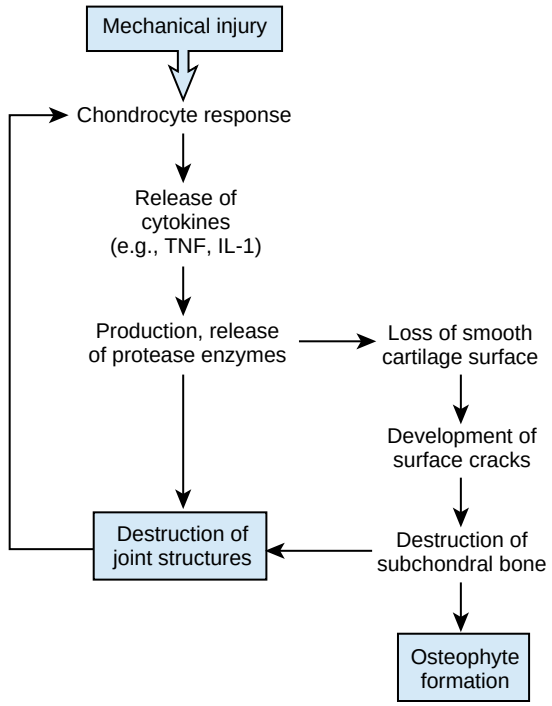
Anatomic or bony disorders
- Hip dysplasia
- Avascular necrosis
- Paget's disease
- Slipped capital femoral epiphysis
- Legg–Calvé–Perthes disease

Metabolic disorders
- Calcium crystal deposition
- Hemochromatosis
- Acromegaly
- Wilson's disease
- Ochronosis

Neuropathic arthritis
- Charcot joint

Hereditary disorders of collagen

Idiopathic or primary variants



■ **FIGURE 43-11** ■ Disease process in osteoarthritis.

common in black women. Obesity is a risk factor for OA of the knee in women and a contributory biomechanical factor in the pathogenesis of the disease. Excess fat may have a direct metabolic effect on cartilage beyond the effects of excess joint stress. Heredity influences the occurrence of hand OA in the DIP joint. Bone mass may also influence the risk of developing OA. In theory, thinner subchondral bone mass may provide a greater shock-absorbing function than denser bone, allowing less direct trauma to the cartilage.

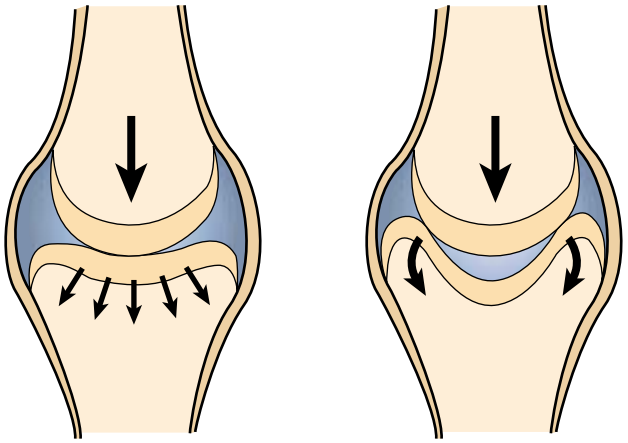
Osteoarthritis is a disorder of the articular cartilage and subchondral bone (*i.e.*, bony plate that supports the articular cartilage) of diarthrodial joints. The joint changes associated with OA are progressive loss of articular cartilage and synovitis resulting from the inflammation caused by the attempts of the bone to remold itself, creating osteophytes or spurs (Fig. 43-11). These changes are accompanied by joint pain, stiffness, limitation of motion, and possibly by joint instability and deformity. Although there may be periods of mild inflammation, it is not the severe, destructive type seen in the inflammatory forms of rheumatic diseases such as RA.

Pathogenesis

The pathogenesis of OA resides in the homeostatic mechanisms that maintain the articular cartilage. Cartilage is a specialized type of connective tissue. As with other types of tissue, it consists of cells (*i.e.*, chondrocytes) nested in an extracellular matrix. In articular cartilage, the extracellular matrix is composed of water, ground substance, collagen, and proteoglycans. The ground substance constitutes a highly hydrated, semisolid gel. Collagen molecules consist of polypeptide chains that form long fibrous strands. The primary function of the collagen fibers is to provide a rigid scaffold to support the chondrocytes and ground substance of cartilage. The proteoglycans, which are large macromolecules made up of disaccharides and amino acids, afford elasticity and stiffness, permitting articular cartilage to resist compression. They also provide a film of interstitial fluid that contributes to the lubrication of the joint. Under high loads such as weight bearing, fluid squeezes out of the cartilage with compression of the opposing surfaces of the joint. The greater the load is, the better the lubrication. With depletion of proteoglycans from the cartilage matrix in OA, the mechanisms that normally operate under high loads to produce a pressurized lubricating film may be impaired.

Articular cartilage plays two essential mechanical roles in joint physiology. First, the articular cartilage serves as a remarkably smooth weight-bearing surface. In combination with synovial fluid, the articular cartilage provides extremely low friction during movement of the joint. Second, the cartilage transmits the load down to the bone, dissipating the mechanical stress. The subchondral bone protects the overlying articular cartilage, providing it with a pliable bed and absorbing the energy of the force (Fig. 43-12).

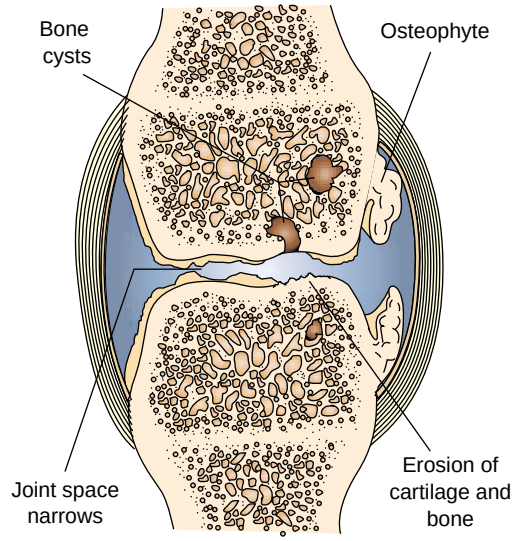
Popularly known as *wear and tear* arthritis, the changes that occur to the articular cartilage in OA are complex. The first recognizable change in OA is edema of the extracellular matrix, principally the intermediate layer. The cartilage loses its smooth aspect, and surface cracks occur allowing synovial fluid to enter and widen the crack. As the crack deepens, the vertical clefts form in the subchondral bone cartilage. Clusters of chondrocytes appear around these clefts and at the surface. Fissures cause fragments of cartilage to become dislodged and enter the articular cavity, creating osteocartilaginous loose bodies and



■ **FIGURE 43-12** ■ (**Left**) A joint normally undergoes deformation of the articular cartilage and the subchondral bone when carrying a load. This maximizes the contact area and spreads the force of the load. (**Right**) If the joint does not deform with a load, the stresses are concentrated and the joint breaks down. (Redrawn from Brandt K.D. & Radin E. [1987]. The physiology of articular stress: Osteoarthroses. *Hospital Practice* [January 15], 111)

uncovering areas of subchondral bone. Sclerosis, or formation of new bone and cysts, usually occurs in the juxta-articular bone (*i.e.*, bone near the joint). New bone that forms at the joint margins is called an *osteophyte*, or spur.

The articular cartilage injury that occurs in OA is thought to result from the release of cytokines such as interleukin-1 and TNF (Fig. 43-13).[18] These chemical messengers stimulate the production and release of proteases (enzymes) that are destructive to joint structures. The resulting damage predisposes the chondrocytes to more injury. The earliest changes in OA are



■ **FIGURE 43-13** ■ Joint changes in osteoarthritis. The left side denotes early changes and joint space narrowing with cartilage breakdown. The right side shows more severe disease progression with lost cartilage and osteophyte formation.

the loss of proteoglycans from the surface of the articular cartilage, followed by death of the chondrocytes. Inadequate repair mechanisms and imbalances between the proteases and their inhibitors may contribute further to disease progression.

Immobilization also can produce degenerative changes in articular cartilage. Cartilage degeneration caused by immobility may result from loss of the pumping action of lubrication that occurs with joint movement. These changes are more marked and appear earlier in areas of contact but occur also in areas not subject to mechanical compression. Although cartilage atrophy is rapidly reversible with activity after a period of immobilization, impact exercise during the period of remobilization can prevent reversal of the atrophy. Thus, slow and gradual remobilization may be an important aspect in preventing cartilage injury. Clinically, it has implications for instructions concerning the recommended level of physical activity after removal of a cast.

Clinical Manifestations

The manifestations of OA may occur suddenly or insidiously. Initially, pain may be described as aching and may be somewhat difficult to localize. It worsens with use or activity and is usually relieved by rest. In later stages of disease activity, pain may be experienced during rest and for several hours after the use of the involved joints. Crepitus and grinding may be evident when the joint is moved. As the disease advances, even minimal activity may cause pain because of the limited range of motion resulting from intra-articular and periarticular structural damage.

The most frequently affected joints are the hips, knees, lumbar and cervical vertebrae, proximal and distal joints of the hand, the first carpometacarpal joint, and the first metatarsophalangeal joints of the feet. A single joint or several may be affected. Although a single weight-bearing joint may be involved initially, other joints often become affected because of the additional stress placed on them while trying to protect the original joint. It is not unusual for a person having a knee replacement to discover soon after the surgery is done that the second knee also needs to be replaced. Other clinical features are limitations of joint motion and joint instability. Joint enlargement usually results from new bone formation; the joint feels hard, in contrast to the soft, spongy feeling characteristic of the joint in RA. Sometimes, mild synovitis or increased synovial fluid can cause joint enlargement.

Diagnosis and Treatment

The diagnosis of OA usually is determined by history and physical examination, x-ray studies, and laboratory findings that exclude other diseases. Although OA often is contrasted with RA for diagnostic purposes, the differences are not always readily apparent. Other rheumatic diseases may be superimposed on OA.

Characteristic radiologic changes initially include medial joint space narrowing, followed by subchondral bony sclerosis, formation of spikes on the tibial eminence, and osteophytes. The results of laboratory studies usually are normal because the disorder is not a systemic disease. The ESR may be slightly elevated in generalized OA or erosive inflammatory variations of the disease. If inflammation is present, there may be a slight increase in the blood cell count. The synovial fluid usually is normal.

Because there is no cure, the treatment of OA is symptomatic and includes physical rehabilitative, pharmacologic, and surgical measures. Physical measures are aimed at improving the supporting structures of the joint and strengthening opposing muscle groups involved in cushioning weight-bearing forces. These include a balance of rest and exercise, use of splints to protect and rest the joint, use of heat and cold to relieve pain and muscle spasm, and adjusting the activities of daily living. The involved joint should not be further abused, and steps should be taken to protect and rest it. This includes weight reduction (when weight-bearing surfaces are involved) and the use of a cane or walker if the hips and knees are involved. Muscle-strengthening exercises may help protect the joint and decrease pain.[34]

Pharmacologic treatment is aimed at reducing inflammation or providing analgesia. The most common medications used in the treatment of OA are the NSAIDs, many of which are available without a prescription. For many persons, acetaminophen in doses as high as 4000 mg/day may be as effective and less toxic than NSAIDs. Corticosteroid injections may be used for relieving symptoms, especially for those who have an effusion of the joint. Injections usually are limited to a total of four and not more than three within 1 year because their use is thought to accelerate joint destruction.[34]

Surgery is considered when the person is having severe pain and joint function is severely reduced. Procedures include arthroscopic lavage and debridement, bunion resections, osteotomies to change alignment of the knee and hip joints, and decompression of the spinal roots in osteoarthritic vertebral stenosis. Total hip replacements have provided effective relief of symptoms and improved range of motion for many persons, as have total knee replacements, although the latter procedure has produced less consistent results.

Crystal-Induced Arthropathies

Crystal deposition in joints produces arthritis. In gout, monosodium urate or uric acid crystals are found in the joint cavity. Another condition in which calcium pyrophosphate dihydrate crystals are found in the joints sometimes is referred to as *pseudogout* or *chondrocalcinosis*. A brief discussion of pseudogout is provided in the section on rheumatic diseases in the elderly.

Gout

Gout is actually a group of diseases known as the *gout syndrome*. It includes acute gouty arthritis with recurrent attacks of severe articular and periarticular inflammation; tophi or the accumulation of crystalline deposits in articular surfaces, bones, soft tissue, and cartilage; gouty nephropathy or renal impairment; and uric acid kidney stones.

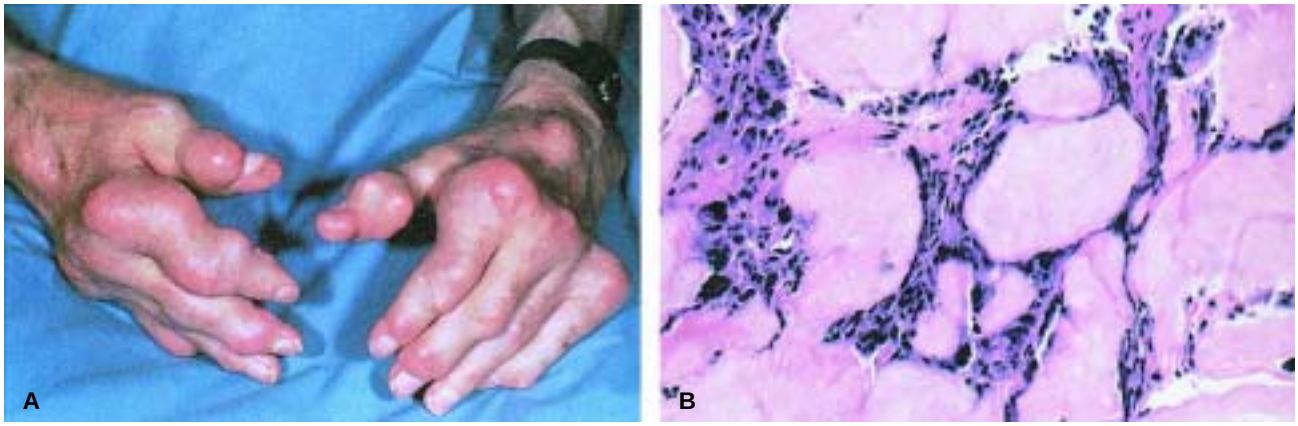
The term *primary gout* is used to designate cases in which the cause of the disorder is unknown or an inborn error in metabolism and is characterized primarily by hyperuricemia and gout. Primary gout is predominantly a disease of men, with a peak incidence in the fourth or sixth decade. In secondary gout, the cause of the hyperuricemia is known but the gout is not the main disorder. Asymptomatic hyperuricemia is a laboratory finding and not a disease. Most persons with hyperuricemia do not develop gout.

Pathogenesis. The pathogenesis of gout resides in an elevation of the serum uric acid levels. Uric acid is the end product of purine (adenine and guanine from DNA and RNA) metabolism.[35] Two pathways are involved in purine synthesis: (1) a de novo pathway, in which purines are synthesized from nonpurine precursors, and (2) the salvage pathway, in which purine bases are recaptured from the breakdown of nucleic acids derived from exogenous (dietary) or endogenous sources. The elevation of uric acid and the subsequent development of gout can result from (1) overproduction of purines, (2) decreased salvage of free purine bases, (3) augmented breakdown of nucleic acids as a result of increased cell turnover, or (4) decreased urinary excretion of uric acid. Primary gout, which constitutes 90% of cases, results from enzyme defects that result in an overproduction of uric acid, inadequate elimination of uric acid by the kidney, or a combination of the two. In most cases, the reason is unknown. In secondary gout the hyperuricemia may be caused by increased breakdown of nucleic acids production, as occurs with rapid tumor cell lysis during treatment for lymphoma or leukemia. Other cases of secondary gout result from chronic renal disease. Some of the diuretics, including the thiazides, can interfere with the excretion of uric acid.

An attack of gout occurs when monosodium urate crystals precipitate in the joint and initiate an inflammatory response. Synovial fluid is a poorer solvent for uric acid than plasma, and uric acid crystals are even less soluble at temperatures below 37°C.[12] Crystal deposition usually occurs in peripheral areas of the body, such as the great toe, where the temperatures are cooler than other parts of the body. With prolonged hyperuricemia, crystals and microtophi accumulate in the synovial lining cells and in the joint cartilage. The released crystals are chemotactic to leukocytes and also activate complement, leading to inflammation and destructive changes to the cartilage and subchondral bone. Repeated attacks of acute arthritis eventually lead to chronic arthritis and the formation of tophi. Tophi are large, hard nodules that have irregular surfaces and contain crystalline deposits of monosodium urate[12] (Fig. 43-14). They are found most commonly in the synovium, olecranon bursa, Achilles tendon, subchondral bone, and extensor surface of the forearm and may be mistaken for rheumatoid nodules. Tophi usually do not appear until 10 years or more after the first gout attack. This stage of gout, called *chronic tophaceous* gout, is characterized by more frequent and prolonged attacks, which often are polyarticular.

Clinical Manifestations. The typical acute attack of gout is monoarticular and usually affects the first metatarsophalangeal joint. The tarsal joints, insteps, ankles, heels, knees, wrists, fingers, and elbows also may be initial sites of involvement. Acute gout often begins at night and may be precipitated by excessive exercise, certain medications, foods, alcohol, or dieting. The onset of pain typically is abrupt, and redness and swelling are observed. The attack may last for days or weeks. Pain may be severe enough to be aggravated even by the weight of a bed sheet covering the affected area.

In the early stages of gout after the initial attack has subsided, the person is asymptomatic, and joint abnormalities are not evident. This is referred to as *intercritical gout*. After the first attack, it may be months or years before another attack. As attacks recur with increased frequency, joint changes occur and become permanent.



■ **FIGURE 43-14** ■ Gout. (**A**) Gouty tophi project from the fingers as rubbery nodules. (**B**) A section from a trophus shows extracellular masses of urate crystals with accompanying foreign-body giant cells. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1404]. Philadelphia: Lippincott Williams & Wilkins)

Diagnosis and Treatment. Although hyperuricemia is the biochemical hallmark of gout, the presence of hyperuricemia cannot be equated with gout because many persons with this condition never develop gout. A definitive diagnosis of gout can be made only when monosodium urate crystals are in the synovial fluid or in tissue sections of tophaceous deposits. Synovial fluid analysis is useful in excluding other conditions, such as septic arthritis, pseudogout, and RA.[36] Diagnostic methods also include measures to determine if the disorder is related to overproduction or to underexcretion of uric acid.

The objectives for treatment of gout include the termination and prevention of the acute attacks of gouty arthritis and the correction of hyperuricemia, with consequent inhibition of further precipitation of sodium urate and absorption of urate crystal deposits already in the tissues. Some changes in lifestyle may be needed, such as maintenance of ideal weight, moderation in alcohol consumption, and avoiding purine-rich foods, such as liver, kidney, sardines, anchovies, and sweetbreads, particularly by persons with excessive tophaceous deposits.

Pharmacologic management of acute gout is directed toward reducing joint inflammation. Hyperuricemia and related problems of tophi, joint destruction, and renal problems are treated after the acute inflammatory process has subsided. NSAIDs, particularly indomethacin and ibuprofen, are used for treating acute gouty arthritis. Alternative therapies include colchicine and intra-articular deposition of corticosteroids. Treatment with colchicine is used early in the acute stage. Colchicine produces its anti-inflammatory effects by inhibition of leukocyte migration and phagocytosis.

Treatment of hyperuricemia is aimed at maintaining normal uric acid levels and is lifelong. Two classes of drugs may be used. Allopurinol prevents the production of uric acid, and uricosuric drugs, such as probenecid or sulfinpyrazone, may be used to prevent the tubular reabsorption of urate and increase its excretion.[30] Prophylactic colchicine or NSAIDs may be used between gout attacks. If the uric acid level is normal and the person has not had recurrent attacks of gout, the use of these medications may be discontinued.[35]

In summary, rheumatoid arthritis is a chronic systemic inflammatory disorder affecting multiple joints. Women are affected more frequently than men. Joint involvement, which is symmetric, begins with inflammatory changes of the synovium and formation of a destructive granulation tissue called *pannus* that leads to joint instability and eventual deformity. Systemic manifestations include weakness, anorexia, weight loss, and low-grade fever. Extra-articular features include rheumatoid nodules and vasculitis.

Systemic lupus erythematosus is a chronic autoimmune disorder that affects multiple body systems. There is no known cause of SLE, but the disease may result from an immunoregulatory disturbance brought about by a combination of genetic, hormonal, and environmental factors. Some drugs have been shown to induce lupus, especially in the elderly. There is an exaggerated production of autoantibodies, which interact with antigens to produce an immune complex. These immune complexes produce an inflammatory response in affected tissues. Systemic sclerosis, often prefixed by the term *progressive*, is sometimes called *scleroderma*. In this disorder, the skin is thickened through fibrosis with an accompanying fixation to the subdermal structures, including the sheaths or fascia covering tendons and muscles.

The spondyloarthropathies affect the axial skeleton, particularly the spine. Inflammation develops at sites where ligaments insert into bone. Because they lack the RF, they are referred to as *seronegative spondyloarthropathies*. They include ankylosing spondylitis, reactive arthritis, and psoriatic arthritis. Ankylosing spondylitis is considered a prototype of this classification category. Bilateral sacroiliitis is the primary feature of ankylosing spondylitis. The disease spectrum ranges from asymptomatic sacroiliitis to a progressive disorder affecting many body systems. The cause remains unknown; however, a strong association between the HLA-B27 antigen and ankylosing spondylitis has been identified. Loss of motion in the spinal column is characteristic of the disease. Peripheral arthritis may occur in some persons.

Osteoarthritis, the most common form of arthritis, is a localized condition affecting primarily the weight-bearing joints. Risk factors for OA progression include older age, OA in multiple joints, neuropathy, and for knees, obesity. The disorder is characterized by degeneration of the articular cartilage and subchondral bone. As cartilage ages, biochemical events such as collagen fatigue and fracture occur with less stress. Attempts at repair by increased matrix synthesis and cellular proliferation maintain the integrity of the cartilage until failure of reparative processes allows the degenerative changes to progress. Pain and stiffness are primary features of the disease. Inflammatory mediators (*e.g.*, prostaglandins) may increase the inflammatory and degenerative response.

Gout is a crystal-induced arthropathy. Acute attacks of arthritis occur with gout and are characterized by the presence of monosodium urate crystals in the joint. The disorder is accompanied by hyperuricemia, which results from overproduction of uric acid or from the reduced ability of the kidney to rid the body of excess uric acid. Management of acute gout is directed first toward the reduction of joint inflammation; then the hyperuricemia is treated. Hyperuricemia is treated with uricosuric agents, which prevent the tubular reabsorption of urate, or with medication that inhibits the production of uric acid.

RHEUMATIC DISEASES IN CHILDREN AND THE ELDERLY

Rheumatic Diseases in Children

Children can be affected with almost all of the rheumatic diseases. In addition to disease-specific differences, these conditions affect not only the child but the family. Growth and development require special attention. Rheumatic disorders of children include juvenile rheumatoid arthritis, systemic lupus erythematosus, and juvenile spondyloarthropathies.

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis (JRA) is a chronic disease that affects approximately 60,000 to 200,000 children in the United States.[18] It is characterized by synovitis and can influence epiphyseal growth by stimulating growth of the affected side. Generalized stunted growth also may occur.

Systemic onset (*i.e.*, Still's disease) affects approximately 20% of children with JRA.[18] The symptoms of Still's disease include a daily intermittent high fever, which usually is accompanied by a rash, generalized lymphadenopathy, hepatosplenomegaly, leukocytosis, and anemia. Most of these children also have joint involvement. Systemic symptoms usually subside in 6 to 12 months. This form of JRA also can make an initial appearance in adulthood. Infections, heart disease, and adrenal insufficiency may cause death.

A second subgroup of JRA, pauciarticular arthritis, affects no more than four joints. This disease affects 55% to 75% of children with JRA. Pauciarticular arthritis affects two distinct groups. The first group generally consists of girls younger than 6 years of age with chronic uveitis. The results of ANA testing in this group usually are positive. The second group, characterized by late-onset arthritis, is made up mostly of boys. The HLA-B27 test results are positive in more than one half of this group. They are affected by sacroiliitis, and the arthritis usually occurs in the lower extremities.

The third subgroup of JRA, accounting for approximately 20% of the total, is polyarticular onset disease. It affects more than four joints during the first 6 months of the disease. This form of arthritis more closely resembles the adult form of the disease than the other two subgroups. RF sometimes is present and may indicate a more active disease process. Systemic features include a low-grade fever, weight loss, malaise, anemia, stunted growth, slight organomegaly (*e.g.*, hepatosplenomegaly), and adenopathy.[18]

The prognosis for most children with rheumatoid arthritis is good. NSAIDs are the first-line drugs used in treating JRA. Salicylates have been replaced by agents such as naproxen, ibuprofen, and ketoprofen. The second-line agent is low-dose methotrexate or, less often, sulfasalazine. Gold salts, hydroxychloroquine, and D-penicillamine rarely are used.[37] Other aspects of treatment of children with JRA are similar to those used for the adult with rheumatoid arthritis. Children are encouraged to lead as normal a life as possible.

Juvenile Spondyloarthropathies

Ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and spondyloarthropathies associated with ulcerative colitis and regional enteritis can affect children and adults. In children, spondyloarthritis manifests in peripheral joints first, mimicking pauciarticular JRA, with no evidence of sacroiliac or spine involvement for months to years after onset. The spondyloarthropathies are more common in boys and commonly occur in children who have a positive family history. HLA-B27 typing is helpful in diagnosing the disease in children because of the unusual presentation of the disease.

Management of the disease involves physical therapy, education, and attention to school and growth and development issues. Medication includes the use of salicylates or other NSAIDs such as tolmetin or indomethacin. More severe disease or symptoms may require systemic corticosteroids.[18]

Rheumatic Diseases in the Elderly

Arthritis is the most common complaint of elderly persons. The pain, stiffness, and muscle weakness affect daily life, often threatening independence and quality of life. Symptoms of the rheumatic diseases also can have an indirect effect and even threaten the duration of life for the elderly. The weakness and gait disturbance that often accompany the rheumatic diseases can contribute to falls and fractures, causing suffering, increased health care costs, further loss of independence, and the potential for a decreased life span.

There are differences in the manifestations, diagnosis, and treatment of some of the rheumatic diseases in the elderly. Older patients often have multiple problems complicating diagnosis and management. The diagnosis of an elderly patient with a musculoskeletal problem must consider a wide variety of disorders that usually are regarded as outside the range of typical rheumatic disease. Among these are metastatic malignancy, multiple myeloma, musculoskeletal disorders accom-

panying endocrine or metabolic disorders, orthopedic conditions, and neurologic disease.

Osteoarthritis is by far the most common form of arthritis among the elderly. It is the greatest cause of disability and limitation of activity in older populations. The prevalence of rheumatoid arthritis increases with advancing age, at least until 75 years of age.[38]

Polymyalgia Rheumatica

Of the various forms of rheumatic disease affecting the elderly, polymyalgia rheumatica is one of the more difficult to diagnose and one of the most important to identify. It is a common syndrome of older patients, rarely occurring before age 50 and usually after age 60 years. Elderly women are especially at risk.

The clinical manifestations of polymyalgia rheumatica include pain and stiffness of the shoulder and pelvic girdle areas. The onset can be abrupt, with the patient going to bed feeling well and awakening with pain and stiffness in the neck, shoulders, and hips. These symptoms may be accompanied by fever, malaise, and weight loss. Because of the shoulder and pelvic area weakness, persons with disorder often have trouble combing their hair, putting on a coat, and getting out of a chair.

A certain percentage of patients with polymyalgia rheumatica also have giant cell arteritis (also called temporal arteritis). The two conditions are considered to represent different manifestations of the same disease. Giant cell arteritis, a form of systemic vasculitis, is a systemic inflammatory disease of large and medium-size arteries (see Chapter 15). It predominantly affects branches of arteries originating from the aortic arch, including the superficial temporal, vertebral, ophthalmic, and posterior ciliary arteries. The disorder often is insidious in onset and may be heralded by the sudden onset of headache, tenderness over the artery, swelling and redness of the overlying skin, blurred vision or diplopia, and facial pain.

The diagnosis of polymyalgia rheumatica is based on the pain and stiffness persisting for at least 1 month and an elevated ESR. The diagnosis is confirmed when the symptoms respond dramatically to a small dose of prednisone, a corticosteroid. For patients with an elevated ESR, the diagnosis usually is based on a 3-day trial of prednisone treatment.[38] People with polymyalgia rheumatica typically exhibit striking clinical improvement approximately the second day. Treatment with NSAIDs provides relief for some patients, but most require continuing therapy with prednisone, with gradual reduction of the dose over the course of 1.5 to 2 years, using the patient's symptoms as the primary guide. Treatment of persons with giant cell arteritis requires use of high-dose prednisone to prevent loss of vision.

Pseudogout

As part of the tissue-aging process, OA develops with associated cartilage degeneration. Calcium pyrophosphate crystals are shed into the joint cavity. These crystals may produce a low-grade chronic inflammation—the chronic pseudogout syndrome. The accumulation of calcium pyrophosphate and related crystalline deposits in articular cartilage is common in the elderly. There are no medications that can remove the crystals from the joints. Although it may be asymptomatic, presence of the crystals may contribute to more rapid cartilage deterioration. This condition may coexist with severe OA.

In summary, rheumatic diseases that affect children can be similar to the adult diseases, but there also are manifestations unique to the younger population. JRA is a chronic disease, characterized by synovitis, that can influence epiphyseal growth. One subgroup of the JRA (Still's disease) presents with systemic manifestations that include a daily intermittent high fever, rash, generalized lymphadenopathy, hepatosplenomegaly, leukocytosis, and anemia. A second subgroup, pauciarticular JRA, affects no more than four joints. The third subgroup of JRA affects more than four joints during the first 6 months of the disease and is similar to the adult form of the disease. Managing rheumatic diseases in children requires a team approach to address issues of the family, school, growth and development, and coping strategies and requires a comprehensive disease management program.

Arthritis is the most common complaint of the elderly population. The pain, stiffness, and muscle weakness affect daily life, often threatening independence and quality of life. There is a difference in the manifestations, diagnosis, and treatment of some of the rheumatic diseases in the elderly compared with those in the younger population. One form of rheumatic disease that has a predilection for the elderly is polymyalgia rheumatica. A certain percentage of patients with polymyalgia rheumatica also have giant cell arteritis, frequently with involvement of the ophthalmic arteries.

REVIEW QUESTIONS

- Describe the roles of osteoclasts and osteoblasts in terms of bone remodeling and relate to the pathogenesis of osteoporosis.
- Explain how factors that affect bone mass during childhood and early adult life influence the risk of osteoporosis, and relate factors such as diet, exercise, and gonadal hormones to the risk of the osteoporosis.
- Describe the pathogenesis and manifestations of osteomalacia and rickets.
- Characterize the cause and manifestations of Paget's disease.
- Describe the difficulty in defining the term *arthritis.*
- Compare rheumatoid arthritis and osteoarthritis in terms of pathogenesis, joint involvement, level of inflammation, and local and systemic manifestations.
- Compare rheumatoid arthritis and osteoarthritis in terms of pathogenesis, joint pathology, and treatment.
- Describe the immunologic process that occurs in systemic lupus erythematosus.
- Contrast and compare ankylosing spondylitis, reactive arthritis, and psoriatic arthritis in terms of cause, pathogenesis, and clinical manifestations.
- Describe the clinical manifestations, diagnostic measures, and methods used in the treatment of gouty arthritis.
- List three types of juvenile rheumatoid arthritis and differentiate among their major characteristics.
- Characterize the manifestations of polymyalgia rheumatica, a common musculoskeletal disorder affecting the elderly.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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