SECTION 1 ORTHOPAEDIC TISSUES

BONE

- Histologic features of bone
  - Types (Fig. 1.1; Table 1.1)
    - Normal bone: lamellar or mature
    - Immature and pathologic bone: woven, more random, more osteocytes, increased turnover, weaker
      - Lamellar bone is stress oriented; woven bone is not.
    - Cortical (compact) bone
      - Constitutes 80% of the skeleton
      - Consists of tightly packed osteons or haversian systems
        - Connected by haversian (or Volkmann) canals
        - Contains arterioles, venules, capillaries, nerves, possibly lymphatic channels
      - Interstitial lamellae: between osteons
      - Fibrils connect lamellae but do not cross cement lines.
      - Cement lines define the outer border of an osteon.
    - Nutrition provided by intraosseous circulation through canals and canaliculi (cell processes of osteocytes)
    - Characterized by slow turnover rate, higher Young’s modulus of elasticity, more stiffness
    - Cancellous bone (spongy or trabecular bone)
      - Less dense, more remodeling according to lines of stress (Wolff’s law)
      - Characterized by high turnover rate, smaller Young’s modulus, more elasticity
  - Cellular biology (Fig. 1.2)
    - Osteoblasts
      - Appear as cuboid cells aligned in layers along immature osteoid
      - Are derived from undifferentiated mesenchymal stem cells
      - These stem cells line haversian canals, endosteum, and periosteum.
      - Become osteoblasts under conditions of low strain and increased oxygen tension
      - Transcription factor RUNX2 and bone morphogenetic protein (BMP) direct mesenchymal cells to the osteoblast lineage.
        - Core-binding factor α-1 and β-catenin also stimulate differentiation into osteoblast
        - Become cartilage under conditions of intermediate strain and low oxygen tension
        - Become fibrous tissue under conditions of high strain
        - Have more endoplasmic reticulum, Golgi apparatus, and mitochondria than do other cells (for synthesis and secretion of matrix)
        - Bone surfaces lined by more differentiated, metabolically active cells
        - Entrapped cells: less active cells in resting regions; maintain the ionic milieu of bone
        - Disruption of the active lining cell layer activates entrapped cells.
    - Receptor-effector interactions in osteoblasts are summarized in Table 1.2.
      - Osteoblasts produce the following:
        - Alkaline phosphatase
        - Osteocalcin (stimulated by 1,25dihydroxyvitamin D [1,25(OH)₂D₃])
        - Type I collagen
        - Bone sialoprotein
        - Receptor activator of nuclear factor (NF)-κβ ligand (RANKL)
        - Osteoprotegerin—binds RANKL to limit its activity
        - Osteoblast activity stimulated by intermittent (pulsatile) exposure to parathyroid hormone (PTH)
• Osteoblast activity inhibited by TNF-α
• Wnts are proteins that promote osteoblast survival and proliferation.
  • Deficient Wnt causes osteopenia; excessive Wnt expression causes high bone mass.
  • Wnts can be sequestered by other secreted molecules such as sclerostin (Scl) and Dickkopf-related protein 1 (Dkk-1).
  • Inhibiting sclerostin or Dkk-1 will lead to increased bone mass

• Osteocytes (see Fig. 1.1)
  • Maintain bone
  • Constitute 90% of the cells in the mature skeleton
  • Former osteoblasts surrounded by newly formed matrix
  • High nucleus/cytoplasm ratio
  • Long interconnecting cytoplasmic processes projecting through the canaliculi
  • Less active in matrix production than osteoblasts
  • Important for control of extracellular calcium and phosphorus concentration

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Table 1.1  Types of Bone

<table>
<thead>
<tr>
<th>MICROSCOPIC APPEARANCE</th>
<th>SUBTYPES</th>
<th>CHARACTERISTICS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamellar</td>
<td>Cortical</td>
<td>Structure is oriented along lines of stress</td>
<td>Femoral shaft</td>
</tr>
<tr>
<td></td>
<td>Cancellous</td>
<td>Strong</td>
<td>Distal femoral metaphysis</td>
</tr>
<tr>
<td></td>
<td>Immature</td>
<td>More elastic than cortical bone</td>
<td>Embryonic skeleton</td>
</tr>
<tr>
<td></td>
<td>Pathologic</td>
<td>Not stress oriented</td>
<td>Fracture callus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Random organization</td>
<td>Osteogenic sarcoma</td>
</tr>
<tr>
<td>Woven</td>
<td></td>
<td>Increased turnover</td>
<td>Fibrous dysplasia</td>
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<tr>
<td></td>
<td></td>
<td>Weak</td>
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<tr>
<td></td>
<td></td>
<td>Flexible</td>
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</tr>
</tbody>
</table>


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Fig. 1.1 Types of bone. Cortical bone consists of tightly packed osteons. Cancellous bone consists of a meshwork of trabeculae. In immature bone, unmineralized osteoid lines the immature trabeculae. Pathologic bone is characterized by atypical osteoblasts and architectural disorganization. (Colorized from Brinker MR, Miller MD: Fundamentals of orthopaedics, Philadelphia, 1999, Saunders, p 2.)
FIG. 1.2 Cellular origins of bone and cartilage cells.

<table>
<thead>
<tr>
<th>Table 1.2</th>
<th>Bone Cell Types, Receptor Types, and Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL TYPE</strong></td>
<td><strong>RECEPTOR</strong></td>
</tr>
<tr>
<td>Osteoblast</td>
<td>PTH</td>
</tr>
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</tr>
<tr>
<td></td>
<td>1,25(OH)₂ vitamin D₃</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins</td>
</tr>
<tr>
<td></td>
<td>Estrogen</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoclast</td>
<td>Calcitonin</td>
</tr>
</tbody>
</table>
- Directly stimulated by calcitonin, inhibited by PTH
- Sclerostin secreted by osteocytes helps negative feedback on osteoblasts’ bone deposition (Fig. 1.3).
  - Differentially regulated according to mechanical loading, with decreased sclerostin in areas of concentrated strain
  - Downregulation is associated with increased bone formation (via sclerostin antibody).
  - Potential for use in fracture healing, bone loss, osseous integration of implants, and genetic bone diseases via upregulation of sclerostin

- Osteoclasts
  - Multinucleated irregular giant cells
  - Derived from hematopoietic cells in macrophage lineage
  - Monocyte progenitors form giant cells by fusion

- Function
  - Bone resorption
    - Bone formation and resorption are linked
    - Stimulated primarily by RANKL binding to RANK receptor on cell surface
  - Osteoblasts (and tumor cells) express RANKL (Fig. 1.4):
    - Binds to receptors on osteoclasts
    - Stimulates differentiation into mature osteoclasts
    - Inhibited by osteoprotegerin (OPG) binding to RANKL.
  - Occurs both normally and in certain conditions, including multiple myeloma and metastatic bone disease
  - Denosumab is a monoclonal antibody that targets and inhibits RANKL binding to the RANK receptor

- Resorption mechanism
  - Border consists of plasma membrane enfoldings that increase surface area
  - Bind to bone surfaces through cell attachment (anchoring) proteins
    - Integrin (αvβ3 or vitronectin receptor)
    - Bone resorption occurs in depressions: Howship lacunae.
    - Effectively seal the space below the osteoclast
    - Synthesize tartrate-resistant acid phosphate
    - Produce hydrogen ions through carbonic anhydrase
    - Lower pH
    - Increase solubility of hydroxyapatite crystals
    - Organic matrix then removed by proteolytic digestion through activity of the lysosomal enzyme cathepsin K

- Signaling
  - Have calcitonin receptors, which inhibit osteoclastic resorption
  - Interleukin-1 (IL-1): potent stimulator of osteoclast differentiation and bone resorption
  - Found in membranes surrounding loose total joint implants
  - In contrast, IL-10 suppresses osteoclasts.

- Matrix (Table 1.3)
  - Organic components: 40% of dry weight of bone
  - Collagen (90% of organic components)
    - Primarily type 1 (mnemonic: bone contains the word one)
      - Type 1 collagen provides tensile strength of bone
      - Hole zones (gaps) exist within the collagen fibril between the ends of molecules.
      - Pores exist between the sides of parallel molecules.
      - Mineral deposition (calcification) occurs within the hole zones and pores.
• Cross-linking decreases collagen solubility and increases its tensile strength.
• Proteoglycans
  • Matrix proteins (noncollagenous)
    • Osteocalcin: most abundant noncollagenous protein in bone
      • Inhibited by PTH and stimulated by 1,25(OH)\(_2\)D\(_3\)
      • Can be measured in serum or urine as a marker of bone turnover
    • Inorganic (mineral) components: 60% of dry weight of bone
      • Calcium hydroxyapatite \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\): provides compressive strength
      • Calcium phosphate (brushite)

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**Tissues surrounding bone**

• Periosteum
  • Connective tissue membrane that covers bone
  • More highly developed in children
  • Inner periosteum, or cambium, is loose and vascular and contains cells capable of becoming osteoblasts.
    • These cells enlarge the diameter of bone during growth and form periosteal callus during fracture healing.
  • Outer (fibrous) periosteum is less cellular and is contiguous with joint capsules.
  • Bone marrow—source of progenitor cells; controls inner diameter of bone
    • Red marrow
      • Hematopoietic (40% water, 40% fat, 20% protein)
      • Slowly changes to yellow marrow with age, first in appendicular skeleton and later in axial skeleton
    • Yellow marrow
      • Inactive (15% water, 80% fat, 5% protein)

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**Table 1.3 Components of Bone Matrix**

<table>
<thead>
<tr>
<th>TYPE OF MATRIX</th>
<th>FUNCTION</th>
<th>COMPOSITION</th>
<th>TYPES</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORGANIC MATRIX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>Provides tensile strength</td>
<td>Primarily type I collagen</td>
<td></td>
<td>Constitutes 90% of organic matrix</td>
</tr>
<tr>
<td>Proteoglycans</td>
<td>Partly responsible for compressive strength</td>
<td>Glycosaminoglycan-protein complexes</td>
<td></td>
<td>Attracts osteoclasts; direct regulation of bone density; most abundant noncollagenous matrix protein (10%–20% of total)</td>
</tr>
<tr>
<td>Matrix proteins</td>
<td>Promote mineralization and bone formation</td>
<td>Osteocalcin (bone (\gamma)-carboxyglutamic acid-containing protein)</td>
<td></td>
<td>Secreted by platelets and osteoblasts; postulated to have a role in regulating calcium or organizing mineral in matrix</td>
</tr>
<tr>
<td>(noncollagenous)</td>
<td></td>
<td>Osteonectin (SPARC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth factors and cytokines</td>
<td>Aid in bone cell differentiation, activation, growth, and turnover</td>
<td>Osteopontin</td>
<td></td>
<td>Cell-binding protein, similar to an integrin</td>
</tr>
<tr>
<td><strong>INORGANIC MATRIX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium hydroxyapatite</td>
<td>Provides compressive strength</td>
<td></td>
<td></td>
<td>Most of the inorganic matrix; primary mineralization in collagen gaps (holes and pores), secondary mineralization on periphery</td>
</tr>
<tr>
<td>[Ca(_{10}(\text{PO}_4)_6(\text{OH})_2]]</td>
<td></td>
<td></td>
<td></td>
<td>Makes up the remaining inorganic matrix</td>
</tr>
<tr>
<td>Osteocalcium phosphate</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(brushite)</td>
<td></td>
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</tr>
</tbody>
</table>
Bone vascular supply
- Bone receives 5%–10% of the cardiac output.
- Bones with a tenuous blood supply include the scaphoid, talus, femoral head, and odontoid.
- Hypoxia, hypercapnia, and sympathectomy increase flow.
- Long bones receive blood from three sources (systems)
  - Nutrient artery system
    - Branch from systemic arteries, enter the diaphyseal cortex through the nutrient foramen, enter the medullary canal, and branch into ascending and descending arteries (Figs. 1.5 and 1.6)
    - Further branch into arterioles in the endosteal cortex, which enables blood supply to at least the inner two-thirds of the mature diaphyseal cortex via the haversian system (see Fig. 1.6)
  - BP in the nutrient artery system is high.
  - 60% of cortical bone vascularized by nutrient arteries
Table 1.4 Types of Bone Formation

<table>
<thead>
<tr>
<th>TYPE OF OSSIFICATION</th>
<th>MECHANISM</th>
<th>EXAMPLES OF NORMAL MECHANISMS</th>
<th>EXAMPLES OF DISEASES WITH ABNORMAL OSSIFICATION</th>
</tr>
</thead>
</table>
| Enchondral           | Bone replaces a cartilage model | Embryonic formation of long bones  
Longitudinal growth (physis)  
Fracture callus  
Bone formed with demineralized bone matrix  
Undifferentiated cells secrete cartilaginous matrix and differentiate into chondrocytes  
Matrix mineralizes and is invaded by vascular buds that bring osteoprogenitor cells.  
Osteoclasts resorb calcified cartilage; osteoblasts form bone.  
Bone replaces the cartilage model; cartilage is not converted to bone.  
Embryonic formation of long bones (Figs. 1.7 and 1.8)  
These bones are formed from the mesenchymal anlage at 6 weeks' gestation.  
Vascular buds invade the mesenchymal model, bringing osteoprogenitor cells that differentiate into osteoblasts and form the primary ossification centers at 8 weeks.  
Differentiation stimulated in part by binding of Wnt protein to the lipoprotein receptor–related protein 5 (LRP5) or LRP6 receptor  
Marrow forms through resorption of the central cartilage anlage by invasion of myeloid precursor cells that are brought in by capillary buds.  
Secondary ossification centers develop at bone ends, forming the epiphyseal centers (growth plates) responsible for longitudinal growth.  
Arterial supply is rich during development, with an epiphyseal artery (terminates in the proliferative zone), metaphyseal arteries, nutrient arteries, and perichondrial arteries (Fig. 1.9). |
| Intramembranous      | Aggregates of undifferentiated mesenchymal cells differentiate into osteoblasts, which form bone | Embryonic flat bone formation  
Bone formation during distraction osteogenesis  
Blastema bone  
Periosteal bone enlargement (width)  
The bone formation phase of bone remodeling | Cleidocranial dysostosis  
Infantile hyperostosis (Caffey disease)  
Melorheostosis |
| Appositional         | Osteoblasts lay down new bone on existing bone | | |
• Reserve zone: cells store lipids, glycogen, and proteoglycan aggregates, decreased oxygen tension occurs in this zone.
• Lysosomal storage diseases (e.g., Gaucher disease) can affect this zone.
• Proliferative zone: growth is longitudinal, with stacking of chondrocytes (the top cell is the dividing “mother” cell), cellular proliferation, and matrix production; increases in oxygen tension and proteoglycans inhibit calcification.
• Achondroplasia causes defects in this zone (see Fig. 1.11).
• Growth hormone exerts its effect in the proliferative zone.
• Hypertrophic zone:
  • Divided into three zones: maturation, degeneration, and provisional calcification.
• Normal matrix mineralization occurs in the lower hypertrophic zone: chondrocytes increase five times in size, accumulate calcium in their mitochondria, die, and release calcium from matrix vesicles.
• Chondrocyte maturation is regulated by systemic hormones and local growth factors (PTH-related peptide inhibits chondrocyte maturation; Indian hedgehog protein is produced by chondrocytes and regulates the expression of PTH-related peptide).
• Osteoblasts migrate from sinusoidal vessels and use cartilage as a scaffolding for bone formation.
• Low oxygen tension and decreased proteoglycan aggregates aid in this process.
• This zone widens in rickets (see Fig. 1.11), with little or no provisional calcification.
**FIG. 1.8** Development of a typical long bone: formation of the growth plate and secondary centers of ossification. (From Netter FH: *CIBA collection of medical illustrations, vol 8: Musculoskeletal system, part I: Anatomy, physiology and developmental disorders*, Basel, Switzerland, 1987, CIBA, p 136.)
CLOSE-UP VIEW OF DEVELOPING EPIPHYSIS AND EPIPHYSEAL GROWTH PLATE

Articular cartilage
Epiphyseal growth plate (poorly organized)
Secondary (epiphyseal) ossification center
Reserve zone
Proliferative zone
Maturation zone
Degeneration zone
Zone of provisional calcification
Primary spongiosa
Secondary spongiosa
Hypertrophic zone
Metaphysis

Epiphyseal artery
Ossification groove of Ranvier
Perichondrial fibrous ring of La Croix
Perichondrial artery
Last intact transverse cartilage septum
Metaphyseal artery
Periosteum
Nutrient artery

Cartilage
Calcified cartilage
Bone

FIG. 1.9 Structure and blood supply of a typical growth plate. (From Netter FH: CIBA collection of medical illustrations, vol 8: Musculoskeletal system, part I: Anatomy, physiology and developmental disorders, Basel, Switzerland, 1987, CIBA, p 166.)
**FIG. 1.10** Zone structure, function, and physiologic features of the growth plate. (From Netter FH: CIBA collection of medical illustrations, vol 8: Musculoskeletal system, part I: Anatomy, physiology and developmental disorders, Basel, Switzerland, 1987, CIBA, p 164.)

<table>
<thead>
<tr>
<th>Zones</th>
<th>Histology</th>
<th>Functions</th>
<th>Blood supply</th>
<th>PO₂</th>
<th>Cell (chondrocyte) health</th>
<th>Cell respiration</th>
<th>Cell glycogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary bony epiphysis Epiphyseal artery</td>
<td>Matrix production</td>
<td>Vessels pass through, do not supply this zone</td>
<td>Poor (low)</td>
<td>Good, active, Much endoplasmic reticulum, vacuoles, mitochondria</td>
<td>Anaerobic</td>
<td>High concentration</td>
<td></td>
</tr>
<tr>
<td>Reserve zone</td>
<td>Storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative zone</td>
<td>Matrix production</td>
<td>Cellular proliferation (longitudinal growth)</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent, Much endoplasmic reticulum, ribosomes, mitochondria</td>
<td>Aerobic</td>
<td>High concentration (less than in above)</td>
</tr>
<tr>
<td>Maturation zone</td>
<td>Preparation of matrix for calcification</td>
<td></td>
<td>Progressive decrease</td>
<td>Poor (low)</td>
<td>Still good</td>
<td>Anaerobic glycolysis</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic zone</td>
<td>Calcification of matrix</td>
<td></td>
<td>Poor (very low)</td>
<td></td>
<td>Cell death</td>
<td>Anaerobic glycolysis</td>
<td></td>
</tr>
<tr>
<td>Zone of provisional calcification</td>
<td>Vascular invasion and resorption of transverse septa</td>
<td>Bone formation</td>
<td>Closed capillary loops</td>
<td>Poor</td>
<td>Good</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Metaphysis</td>
<td>Remodeling Internal removal of cartilage bars, replacement of fiber bone with lamellar bone External: funnelization</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Aerobic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zones</td>
<td>Histology</td>
<td>Functions</td>
<td>Exemplary diseases</td>
<td>Defect (if known)</td>
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<tr>
<td>Secondary bony epiphysis</td>
<td>Matrix production</td>
<td>Diastrophic dwarfism</td>
<td>Defective type II collagen synthesis</td>
<td></td>
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<td></td>
<td>Storage</td>
<td>Pseudoachondroplasia</td>
<td>Defective processing and transport of proteoglycans</td>
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<tr>
<td></td>
<td></td>
<td>Kneist syndrome</td>
<td>Defective processing of proteoglycans</td>
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<tr>
<td>Reserve zone</td>
<td></td>
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</tr>
<tr>
<td>Proliferative zone</td>
<td>Matrix production</td>
<td>Gigantism</td>
<td>Increased cell proliferation</td>
<td></td>
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<tr>
<td></td>
<td>Cellular proliferation</td>
<td>Achondroplasia</td>
<td>Deficiency of cell proliferation</td>
<td></td>
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<tr>
<td></td>
<td>(longitudinal growth)</td>
<td>Hypochondroplasia</td>
<td>Less severe deficiency of cell proliferation</td>
<td></td>
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<tr>
<td>Maturation zone</td>
<td>Preparation of matrix for</td>
<td>Mucopolysaccharidosis</td>
<td>Deficiencies of specific lysosomal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>calcification</td>
<td>(Morquio syndrome,</td>
<td>acid hydrolases, with lysosomal</td>
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<tr>
<td></td>
<td></td>
<td>Hurter syndrome)</td>
<td>storage of mucopolysaccharides</td>
<td></td>
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<tr>
<td>Degenerative zone</td>
<td></td>
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<tr>
<td>Zone of provisional</td>
<td>Calcification of matrix</td>
<td>Rickets, osteomalacia</td>
<td>Insufficiency of Ca(^{2+}) and/or</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>calcification</td>
<td></td>
<td>(also, defects in metaphysis)</td>
<td>for normal calcification of matrix</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metaphysis</td>
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<tr>
<td>Primary spongiosa</td>
<td>Vascular invasion and</td>
<td>Metaphyseal chondrodysplasia</td>
<td>Extension of hypertrophic cells into</td>
<td></td>
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<tr>
<td></td>
<td>resorption of transverse</td>
<td>(Jansen and Schmid types)</td>
<td>metaphysis</td>
<td></td>
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<td></td>
<td>septa</td>
<td>Acute hematogenous osteomyelitis</td>
<td>Flourishing of bacteria due to sluggish circulation, low PO(_2) reticuloendothelial deficiency</td>
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<tr>
<td>Secondary spongiosa</td>
<td>Bone formation</td>
<td>Osteopetrosis</td>
<td>Abnormality of osteoclasts (internal remodeling)</td>
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<tr>
<td></td>
<td></td>
<td>Osteogenesis imperfecta</td>
<td>Abnormality of osteoblasts and collagen synthesis</td>
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<tr>
<td></td>
<td></td>
<td>Scurvy</td>
<td>Inadequate collagen formation</td>
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<tr>
<td></td>
<td></td>
<td>Metaphyseal dysplasia</td>
<td>Abnormality of funnelization (external remodeling)</td>
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</tbody>
</table>

FIG. 1.11 Zone structure and pathologic defects of cellular metabolism. (From Netter FH: CIBA collection of medical illustrations, vol 8: Musculoskeletal system, part I: Anatomy, physiology and developmental disorders, Basel, Switzerland, 1987, CIBA, p 165.)
- Mucopolysaccharide diseases (see Fig. 1.11) affect this zone, leading to chondrocyte degeneration.
- **Physal fractures probably traverse several zones, depending on the type of loading (Fig. 1.12).**
- Slipped capital femoral epiphysis (SCFE) occurs here.
  - Except renal osteodystrophy (through metaphyseal spongiosa).

**Metaphysis**
- Adjacent to the physis and expands with skeletal growth
- Osteoblasts from osteoprogenitor cells align on cartilage bars produced by physeal expansion.
- Primary spongiosa (calcified cartilage bars) mineralizes to form woven bone and remodels to form secondary spongiosa and a “cutback zone” at the metaphysis.
- **Groove of Ranvier:** supplies chondrocytes to the periphery for lateral growth (width)
- Perichondrial ring of La Croix: dense fibrous tissue, primary membrane anchoring the periphery of the physis
- Intramembranous ossification
  - Occurs without a cartilage model
  - Undifferentiated mesenchymal cells aggregate into layers (or membranes), differentiate into osteoblasts, and deposit an organic matrix that mineralizes.
  - Examples:
    - Embryonic flat bone formation
    - Bone formation during distraction osteogenesis
    - Blastema bone (in young children with amputations)
- Appositional ossification
  - Osteoblasts align on the existing bone surface and lay down new bone.
  - Examples:
    - Periosteal bone enlargement (width)
    - Bone formation phase of bone remodeling

**Bone remodeling**
- General
  - Cortical bone and cancellous bone are continuously remodeled throughout life by osteoclastic and osteoblastic activity (Fig. 1.13).
- **Wolff's law: remodeling occurs in response to mechanical stress**
  - Increasing mechanical stress increases bone gain.
  - Removing external mechanical stress increases bone loss, which is reversible (to varying degrees) on remobilization.
  - Piezoelectric remodeling occurs in response to electric charge.
  - The compression side of bone is electronegative, stimulating osteoblasts (formation).
  - The tension side of bone is electropositive, stimulating osteoclasts (resorption).
- **Hueter-Volkmann law:** remodeling occurs in small packets of cells known as basic multicellular units (BMUs).
  - Such remodeling is modulated by hormones and cytokines.
- Compressive forces inhibit growth; tension stimulates it.
  - Suggests that mechanical factors influence longitudinal growth, bone remodeling, and fracture repair.
  - May play a role in scoliosis and Blount disease.
  - Cortical bone remodeling.
    - Osteoclastic tunneling (cutting cones; Fig. 1.14)
    - The head of the cutting cone is made up of osteoclasts followed by capillaries and osteoblasts.
    - Followed by layering of osteoblasts and successive deposition of layers of lamellae.
  - Cancellous bone remodeling
    - Osteoclastic resorption followed by deposition of new bone by osteoblasts

**Bone injury and repair**
- Fracture repair (Table 1.5)
  - Stages of fracture repair
  - Inflammation
    - Fracture hematoma provides hematopoietic cells capable of secreting growth factors.
    - Subsequently, fibroblasts, mesenchymal cells, and osteoprogenitor cells form granulation tissue around the fracture ends.
    - Osteoblasts (from surrounding osteogenic precursor cells) and fibroblasts proliferate.
  - Repair
    - Primary callus response within 2 weeks
    - For bone ends not in continuity, bridging (soft) callus occurs.
      - Soft callus is later replaced through enchondral ossification by woven bone (hard callus).
      - Medullary callus supplements the bridging callus, forming more slowly and later.
    - Fracture healing varies with treatment method (Table 1.6).
In an unstable fracture, type II collagen is expressed early, followed by type I collagen.

Amount of callus is inversely proportional to extent of immobilization.

Progenitor cell differentiation
- High strain promotes development of fibrous tissue.
- Low strain and high oxygen tension promote development of woven bone.
- Intermediate strain and low oxygen tension promote development of cartilage.

Remodeling
- Remodeling begins in middle of repair phase and continues long after clinical healing (up to 7 years).
- Allows bone to assume its normal configuration and shape according to stress exposure (Wolff's law)
- Throughout, woven bone is replaced with lamellar bone.
- Fracture healing is complete when the marrow space is repopulated.

Biochemistry of fracture healing (Table 1.7)
- Growth factors of bone (Table 1.8)
  - BMP-2: acute open tibial fractures
  - BMP-3: no osteogenic activity
  - BMP-4: associated with fibrodysplasia ossificans progressiva
  - BMP-7: tibial nonunions
- BMPs activate intracellular signal molecules called SMADs to cause osteoblastic differentiation

Endocrine effects on fracture healing (Table 1.9)
- Head injury
  - Can increase the osteogenic response to fracture
- Nicotine (smoking)
  - Increases time to fracture healing
  - Increases risk of nonunion (particularly in the tibia)
  - Decreases strength of fracture callus
  - Decreases risk of pseudarthrosis after lumbar fusion by up to 500%
  - Nonsteroidal antiinflammatory drugs
    - Have adverse effects on fracture healing and healing of lumbar spinal fusions
  - Cyclooxygenase-2 (COX-2) activity is required for normal enchondral ossification during fracture healing.
  - Quinolone antibiotics
    - Toxic to chondrocytes and inhibit fracture healing
  - Ultrasound and fracture healing
    - Low-intensity pulsed ultrasound (30 mW/cm²) accelerates fracture healing and increases the mechanical strength of callus
    - A cellular response to the mechanical energy of ultrasound has been postulated.

Effect of radiation on bone
- High-dose irradiation causes long-term changes within the haversian system and decreases cellularity.

Diet and fracture healing
- Protein malnutrition results in negative effects on fracture healing:
  - Decreased periosteal and external callus
  - Decreased callus strength and stiffness
  - Increased fibrous tissue within callus
- In experimental models, oral supplementation with essential amino acids improves bone mineral density in fracture callus.

FIG. 1.13 Bone remodeling. Osteoclasts dissolve the mineral from the bone matrix. Osteoblasts produce new bone (osteoid) that fills in the resorption pit. Some osteoblasts are left within the bone matrix as osteocytes. (From Firestein GS et al, editors: Kelley's textbook of rheumatology, ed 8, Philadelphia, 2008, Saunders.)
- Electricity and fracture healing
- Definitions
  - Stress-generated potentials
  - Piezoelectric effect: tissue charges are displaced secondary to mechanical forces.
- Streaming potentials: occur when electrically charged fluid is forced over a cell membrane that has a fixed charge
- Transmembrane potentials: generated by cellular metabolism

![Diagram of Cortical Bone Remodeling](image)

**FIG. 1.14** Cortical bone remodeling. (A) Longitudinal and cross sections of a timeline illustrating formation of an osteon. Osteoclasts cut a cylindrical channel through bone. Osteoblasts follow, laying down bone on the surface of the channel until matrix surrounds the central blood vessel of the newly formed osteon (closing cone of a new osteon). (B) Photomicrograph of a cutting cone. (C) Higher-magnification photomicrograph; osteoclastic resorption can be more clearly appreciated. (A from Standring S et al, editors: Functional anatomy of the musculoskeletal system. In *Gray's anatomy*, ed 40, London, 2008, Elsevier, Fig. 5-19.)
- Types of electrical stimulation
  - Direct current: stimulates an inflammatory-like response, resulting in decreased oxygen concentrations and increase in tissue pH (similar to effects of an implantable bone stimulator).
  - Alternating current: “capacity-coupled generators”; affects cyclic AMP (cAMP) synthesis, collagen synthesis, and calcification during repair stage
  - Pulsed electromagnetic fields (PEMFs): initiate calcification of fibrocartilage (but not fibrous tissue)

**Bone grafting** (Table 1.10)

- Graft properties
  - **Osteoconductive matrix**: acts as a scaffold or framework for bone growth
  - **Osteoinductive factors**: growth factors (BMP) that stimulate bone formation
  - **Osteogenic cells**: primitive mesenchymal cells, osteoblasts, and osteocytes
  - **Structural integrity**

- Specific bone graft types
  - **Cortical bone graft**
    - Slower incorporation: remodels existing haversian systems through resorption (weakens the graft) and then deposits new bone (restores strength)
    - Resorption confined to osteon borders; interstitial lamellae are preserved.
    - Used for structural defects
    - Insufficiency fracture eventually occurs in 25% of massive grafts.
  - **Cancellous graft**
    - Useful for grafting nonunion and cavitary defects
    - Revascularizes and incorporates quickly
    - Osteoblasts lay down new bone on old trabeculae, which are later remodeled (“creeping substitution”).

**Table 1.5** Biologic and Mechanical Factors Influencing Fracture Healing

<table>
<thead>
<tr>
<th>Biologic factors</th>
<th>Mechanical factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>Soft tissue attachments to bone</td>
</tr>
<tr>
<td>Comorbid medical conditions</td>
<td>Stability (extent of immobilization)</td>
</tr>
<tr>
<td>Functional level</td>
<td>Anatomic location</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Level of energy imparted</td>
</tr>
<tr>
<td>Nerve function</td>
<td>Extent of bone loss</td>
</tr>
<tr>
<td>Vascular injury</td>
<td></td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
</tr>
<tr>
<td>Growth factors</td>
<td></td>
</tr>
<tr>
<td>Health of the soft tissue envelope</td>
<td></td>
</tr>
<tr>
<td>Sterility (in open fractures)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td></td>
</tr>
<tr>
<td>Local pathologic conditions</td>
<td></td>
</tr>
<tr>
<td>Level of energy imparted</td>
<td></td>
</tr>
<tr>
<td>Type of bone affected</td>
<td></td>
</tr>
<tr>
<td>Extent of bone loss</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.6** Type of Fracture Healing Based on Type of Stabilization

<table>
<thead>
<tr>
<th>TYPE OF STABILIZATION</th>
<th>PREDOMINANT TYPE OF HEALING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cast (closed treatment)</td>
<td>Periosteal bridging callus and interfragmentary enchondral ossification</td>
</tr>
<tr>
<td>Compression plate</td>
<td>Primary cortical healing (cutting-cone type or haversian remodeling)</td>
</tr>
<tr>
<td>Intramedullary nail</td>
<td>Early: periosteal bridging callus; enchondral ossification</td>
</tr>
<tr>
<td></td>
<td>Late: medullary callus and intramembranous ossification</td>
</tr>
<tr>
<td>External fixator</td>
<td>Dependent on extent of rigidity:</td>
</tr>
<tr>
<td></td>
<td>Less rigid: periosteal bridging callus; enchondral ossification</td>
</tr>
<tr>
<td></td>
<td>More rigid: primary cortical healing; intramembranous ossification</td>
</tr>
<tr>
<td>Inadequate immobilization with adequate blood supply</td>
<td>Hypertrophic nonunion (failed enchondral ossification); type II collagen predominates</td>
</tr>
<tr>
<td>Inadequate immobilization without adequate blood supply</td>
<td>Atrophic nonunion</td>
</tr>
<tr>
<td>Inadequate reduction with displacement at the fracture site</td>
<td>Oligotrophic nonunion</td>
</tr>
</tbody>
</table>

**Table 1.7** Biochemical Steps of Fracture Healing

<table>
<thead>
<tr>
<th>STEP</th>
<th>COLLAGEN TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenchymal</td>
<td>I, II, III, V</td>
</tr>
<tr>
<td>Chondroid</td>
<td>II, IX</td>
</tr>
<tr>
<td>Chondroid-osteoid</td>
<td>I, II, X</td>
</tr>
<tr>
<td>Osteogenic</td>
<td>I</td>
</tr>
</tbody>
</table>

**Table 1.8** Growth Factors of Bone

<table>
<thead>
<tr>
<th>GROWTH FACTOR</th>
<th>ACTION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone morphogenetic protein</td>
<td>Osteoinductive; stimulates bone formation</td>
<td>Target cells of BMP are the undifferentiated perivascular mesenchymal cells; signals through serine-threonine kinase receptors</td>
</tr>
<tr>
<td></td>
<td>Induces metaplasia of mesenchymal cells into osteoblasts</td>
<td>Intraacellular molecules called SMADs serve as signaling mediators for BMPs</td>
</tr>
<tr>
<td>Transforming growth factor–β</td>
<td>Induces mesenchymal cells to produce type II collagen and proteoglycans</td>
<td>Found in fracture hematomas; believed to regulate cartilage and bone formation in fracture callus; signals through serine/threonine kinase receptors</td>
</tr>
<tr>
<td></td>
<td>Induces osteoblasts to synthesize collagen</td>
<td>Coating porous implants with TGF-β enhances bone ingrowth</td>
</tr>
<tr>
<td>IGF-2</td>
<td>Stimulates type I collagen, cellular proliferation, cartilage matrix synthesis, and bone formation</td>
<td>Signals through tyrosine kinase receptors</td>
</tr>
<tr>
<td>Platelet-derived growth factor</td>
<td>Attracts inflammatory cells to the fracture site (chemoattractant)</td>
<td>Released from platelets; signals through tyrosine kinase receptors</td>
</tr>
</tbody>
</table>
- Vascularized bone graft
  - Although technically difficult to implant, allows more rapid union and cell preservation; best for irradiated tissues or large tissue defects (morbidity may occur at donor site [e.g., fibula])
- Nonvascular bone grafts are more common
- Allograft bone
  - Types
    - Fresh: increased immunogenicity
    - Fresh frozen: less immunogenic than fresh; BMP preserved
    - Freeze dried (lyophilized “croutons”): loses structural integrity and depletes BMP, is least immunogenic, is purely osteoconductive, has lowest risk of viral transmission
  - Bone matrix gelatin (a digested source of BMP): demineralized bone matrix is osteoconductive and osteoinductive.
  - Osteoarticular (osteochondral) allograft
    - Immunogenic (cartilage is vulnerable to inflammatory mediators of immune response)
    - Articular cartilage preserved with glycerol or DMSO
    - Cryogenically preserved grafts (leave few viable chondrocytes)
    - Tissue-matched (syngeneic) osteochondral grafts (produce minimal immunogenic effects and incorporate well)
  - Antigenicity
    - Allograft bone possesses a spectrum of potential antigens, primarily from cell surface glycoproteins.
    - Classes I and II cellular antigens in allograft are recognized by T lymphocytes in the host.

Table 1.9 Endocrine Effects on Fracture Healing

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>EFFECT</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>−</td>
<td>Decreased callus proliferation</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>±</td>
<td>Unknown</td>
</tr>
<tr>
<td>Thyroid hormone, PTH</td>
<td>+</td>
<td>Bone remodeling</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>+</td>
<td>Increased callus volume</td>
</tr>
</tbody>
</table>

Table 1.10 Types of Bone Grafts and Bone Graft Properties

<table>
<thead>
<tr>
<th>GRAFT</th>
<th>OSTEOCONDUCTION</th>
<th>OSTEOINDUCTION</th>
<th>OSTEOGENIC CELLS</th>
<th>STRUCTURAL INTEGRITY</th>
<th>OTHER PROPERTIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autograft</td>
<td>Excellent</td>
<td>Good</td>
<td>Excellent</td>
<td>Poor</td>
<td>Rapid incorporation</td>
</tr>
<tr>
<td>Cancellous</td>
<td>Fair</td>
<td>Fair</td>
<td>Fair</td>
<td>Good</td>
<td>Slow incorporation</td>
</tr>
<tr>
<td>Cortical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fresh has the highest immunogenicity</td>
</tr>
<tr>
<td>Allograft</td>
<td>Fair</td>
<td>Fair</td>
<td>Fair</td>
<td>Poor</td>
<td>Freeze dried is the least immunogenic but has the least structural integrity (weakest)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>Good</td>
<td>Fresh frozen preserves BMP</td>
</tr>
<tr>
<td>Ceramics</td>
<td>Fair</td>
<td>None</td>
<td>None</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Demineralized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bone matrix</td>
<td>Good</td>
<td>Fair</td>
<td>None</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Poor</td>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>

- Aluminum oxide: alumina ceramic bonds to bone in response to stress and strain between implant and bone
- Five stages of graft healing (Urist) are listed in Table 1.11.
- Distraction osteogenesis
  - Definition: distraction-stimulated formation of bone
  - Clinical applications:
    - Limb lengthening
    - Deformity correction (via differential lengthening)
    - Segmental bone loss (via bone transport)
  - Biologic features:
    - Under optimal stability, intramembranous ossification occurs.
    - Under instability, bone forms through enchondral ossification.
    - Under extreme instability, pseudarthrosis may occur.
- Three histologic phases:
  - Latency phase (5–7 days)
  - Distraction phase (1 mm/day |≈ 1 inch/mo|)
  - Consolidation phase (typically twice as long as distraction phase)
- Optimal conditions during distraction osteogenesis:
  - Low-energy corticotomy/osteotomy
  - Minimal soft tissue stripping at corticotomy site (preserves blood supply)
  - Stable external fixation and elimination of torsion, shear, and bending moments
  - Latency period (no lengthening) 5–7 days
  - Distraction: 0.25 mm three or four times per day (0.75–1.0 mm/day)
  - Neutral fixation interval (no distraction) during consolidation
  - Normal physiologic use of the extremity, including weight bearing
- Heterotopic ossification
  - Ectopic bone forms in soft tissues.
  - Most commonly in response to injury or surgical dissection
  - Myositis ossificans: heterotopic ossification in muscle
  - Increased risk with traumatic brain injury
  - Recurrence after resection is likely if neurologic compromise is severe.
  - Timing of surgery for heterotopic ossification after traumatic brain injury is important:
    - Time since injury (3–6 months)
    - Evidence of bone maturation on radiographs (sharp demarcation, trabecular pattern)
  - Heterotopic ossification may be resected after total hip arthroplasty (THA).
  - Rejection should be delayed for 6 months or longer after THA.
  - Adjuvant radiation therapy may prevent recurrence of heterotopic ossification.
- Optimal therapy: single preoperative or postoperative dose of 600–800 rad/cGy (6–8 Gy)
- Prevents proliferation and differentiation of primordial mesenchymal cells into osteoprogenitor cells
- Preoperative radiation (600–800 rad/cGy) may be given in a single fraction up to 24 hours prior to surgery.
- Helps prevent heterotopic ossification after THA in patients at high risk for this development
- Incidence of heterotopic ossification after THA among patients with Paget disease is approximately 50%.

### Table 1.11 Stages of Graft Healing

<table>
<thead>
<tr>
<th>STAGE</th>
<th>ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Chemotaxis stimulated by necrotic</td>
</tr>
<tr>
<td></td>
<td>debris</td>
</tr>
<tr>
<td>Osteoinduction</td>
<td>From precursors</td>
</tr>
<tr>
<td>Osteoconduction</td>
<td>Osteoblast and osteoclast function</td>
</tr>
<tr>
<td>Remodeling</td>
<td>New bone forming over scaffold</td>
</tr>
<tr>
<td></td>
<td>Process continues for years</td>
</tr>
</tbody>
</table>

### Normal bone metabolism

#### Calcium
- Important in muscle and nerve function, clotting, and many other areas
- More than 99% of the body's calcium is stored in bones.
  - Plasma calcium is about equally free and bound (usually to albumin).
  - Approximately 400 mg of calcium is released from bone daily.
- Absorbed in the duodenum by active transport
  - Requires ATP and calcium-binding protein
  - Regulated by 1,25(OH)₂D₃
- Absorbed in the jejunum by passive diffusion
- Kidney reabsorbs 98% of calcium (60% in proximal tubule)
  - Calcium may be excreted in stool.
- Primary homeostatic regulators of serum calcium are PTH and 1,25(OH)₂D₃
- Dietary requirement for elemental calcium:
  - Approximately 600 mg/day for children
  - Approximately 1300 mg/day for adolescents and young adults (ages 10–25 years)
  - 750 mg/day for adults ages 25–50 years
  - 1200–1500 for adults over age 50 years
  - 1500 mg/day for pregnant women
  - 2000 mg/day for lactating women
  - 1500 mg/day for postmenopausal women and for the patient with a healing fracture in a long bone
- Calcium balance is usually positive in the first three decades of life and negative after the fourth decade.

#### Phosphate
- A key component of bone mineral
  - Approximately 85% of the body's phosphate stores are in bone.
- Plasma phosphate is mostly unbound.
- Also important in enzyme systems and molecular interactions as a metabolite and buffer
- Dietary intake of phosphate is usually adequate.
- Daily requirement is 1000–1500 mg.
- Reabsorbed by the kidney (proximal tubule)
- Phosphate may be excreted in urine.
- Parathyroid hormone
  - An 84-amino acid peptide
  - Synthesized in and secreted from chief cells of the (four) parathyroid glands
  - N-terminal fragment 1–34 is the active portion.
  - Teriparatide, the synthetic form of recombinant human PTH, contains this active sequence.
    - Used to treat some forms of osteoporosis
    - Increased risk of osteosarcoma
- Effect of PTH mediated by the cAMP second-messenger mechanism downstream in osteocytes
- PTH helps regulate plasma calcium.
  - Decreased calcium levels in extracellular fluid stimulate β2 adrenoreceptors to release PTH, which acts at the intestines, kidneys, and bones (Table 1.12).
- PTH directly activates osteoblasts.
- PTH modulates renal phosphate filtration.
- PTH may accentuate bone loss in elderly persons.
- PTH-related protein and its receptor have been implicated in metaphyseal dysplasia.

**Vitamin D**
- Naturally occurring steroid
  - Activated by ultraviolet radiation from sunlight or utilized from dietary intake (Fig. 1.15)
  - Hydroxylated to 25(OH)D in the liver and hydroxylated a second time in the kidney to one of the following:
    - 1,25(OH)2D3, the active hormone
    - 24,25(OH)2D3, the inactive form (Fig. 1.16)
  - 1,25(OH)2D3 works at the intestines, kidneys, and bones (see Table 1.12).
- Phenytoin (Dilantin) impairs metabolism of vitamin D.

**Calcitonin**
- A 32–amino acid peptide hormone produced by clear cells in the parafollicles of the thyroid gland
  - Limited role in calcium regulation (see Table 1.12)
  - Increased extracellular calcium levels cause secretion of calcitonin.
    - Controlled by a β2 receptor
    - Inhibits osteoclastic bone resorption
    - Osteoclasts have calcitonin receptors.
    - Calcitonin decreases osteoclast number and activity.
    - Decreases serum calcium level
  - May also have a role in fracture healing and in reducing vertebral compression fractures in high-turnover osteoporosis

**Other hormones affecting bone metabolism**
- Estrogen
  - Prevents bone loss by inhibiting bone resorption
    - Decrease in urinary pyridinoline cross-links
  - Because bone formation and resorption are coupled, estrogen therapy also decreases bone formation.
  - Supplementation is helpful in postmenopausal women only if started within 5–10 years after onset of menopause.
  - Risk of endometrial cancer is reduced when estrogen therapy is combined with cyclic progestin therapy.
  - Certain regimens of hormone replacement therapy may increase risks of heart disease and breast cancer.
  - Other postmenopausal pharmacologic interventions (alendronate, raloxifene) should be strongly considered.
- Corticosteroids
  - Increase bone loss
    - Decrease gut absorption of calcium by decreasing binding proteins
    - Decrease bone formation (cancellous more than cortical) by inhibiting collagen synthesis and osteoblast productivity
    - Do not affect mineralization
    - Alternate-day therapy may reduce the effects.
- Thyroid hormones
  - Affect bone resorption more than bone formation
    - Large (thyroid-suppressive) doses of thyroxine can lead to osteoporosis.
    - Regulates skeletal growth at the physis
    - Stimulates chondrocyte growth, type X collagen synthesis, and alkaline phosphatase activity
- Growth hormone
  - Causes positive calcium balance by increasing gut absorption of calcium more than it increases urinary excretion
• Insulin and somatomedins participate in this effect.
• Growth factors
  • Transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), monokines, and lymphokines have roles in bone and cartilage repair.

Peak bone mass
• Believed to occur between 16 and 25 years of age
• Higher in men and in African Americans
• After peak, bone loss occurs at a rate of 0.3%–0.5% per year
• Rate of bone loss is 2%–3% per year in untreated women during the sixth through tenth years after menopause.

• Affects trabecular more than cortical bone
  • Increase in trabecular rods results in increased anisotropy.
• Cortical bone becomes thinner and intracortical porosities increase.
• Cortical bone becomes more brittle, less strong, and less stiff.
• Long bones have greater inner and outer diameters.

Bone loss
• Occurs at the onset of menopause when both bone formation and resorption are accelerated
• A net negative change in calcium balance: menopause decreases intestinal absorption and increases urinary excretion of calcium.
• Both urinary hydroxyproline and pyridinoline cross-links are elevated when bone resorption occurs.
• Serum alkaline phosphatase level is elevated when bone formation is increased.

Conditions of bone mineralization (Tables 1.13 through 1.17)

Hypercalcemia
• Can manifest in a number of ways
• Polyuria, polydipsia, and nephrolithiasis
• Excessive bony resorption with or without fibrotic tissue replacement (ostitis fibrosa cystica)
• CNS effects (confusion, stupor, weakness)
• GI effects (constipation)
• Can also cause anorexia, nausea, vomiting, dehydration, and muscle weakness
• Primary hyperparathyroidism
• Overproduction of PTH usually a result of a parathyroid adenoma (surgical parathyroidectomy is curative)
• Generally affects only one parathyroid gland
• Reflected in a net increase in plasma calcium and a decrease in plasma phosphate (as a result of enhanced urinary excretion)

Table 1.13 Overview of Clinical and Radiographic Aspects of Metabolic Bone Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CAUSE</th>
<th>CLINICAL FINDINGS</th>
<th>RADIOGRAPHIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>PTH overproduction: adenoma</td>
<td>Kidney stone, hyperreflexia</td>
<td>Osteopenia, osteitis fibrosa cystica</td>
</tr>
<tr>
<td>Familial syndromes</td>
<td>PTH overproduction: MEN/renal</td>
<td>Endocrine and renal abnormalities</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>PTH underproduction: idiopathic</td>
<td>Neuromuscular irritability, cataracts</td>
<td>Calcified basal ganglia</td>
</tr>
<tr>
<td>PHP/Albright syndrome</td>
<td>PTH receptor abnormality</td>
<td>Short MC/MT, obesity</td>
<td>Brachydactyly, exostosis</td>
</tr>
<tr>
<td>Renal osteodystrophy</td>
<td>Chronic renal failure: ↓ phosphate excretion</td>
<td>Renal abnormalities</td>
<td>Rugger jersey spine</td>
</tr>
<tr>
<td>Rickets (osteomalacia)</td>
<td>↓ Vitamin D diet; malabsorption</td>
<td>Bone deformities, hypotonia</td>
<td>Rickets, poor mineralization</td>
</tr>
<tr>
<td>Vitamin D–deficiency rickets</td>
<td>See Table 1.16</td>
<td>Total baldness</td>
<td>Poor mineralization</td>
</tr>
<tr>
<td>Vitamin D–dependent (types I and II) rickets</td>
<td>↓ Renal tubular phosphate resorption</td>
<td>Bone deformities, hypotonia</td>
<td>Poor mineralization</td>
</tr>
<tr>
<td>Vitamin D–resistant (hypophosphatemic) rickets</td>
<td>↓ Alkaline phosphatase</td>
<td>Bone deformities, hypotonia</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>↓ Estrogen: ↓ bone mass</td>
<td>Kyphosis, fractures</td>
<td>Compression vertebral fractures, hip fractures</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Osteoporosis</td>
<td></td>
<td>Thin cortices, corner sign</td>
</tr>
<tr>
<td>Scurvy</td>
<td>Vitamin C deficiency: defective collagen</td>
<td>Fatigue, bleeding, effusions</td>
<td></td>
</tr>
<tr>
<td>Osteodensity</td>
<td>Paget disease of bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteopenosis</td>
<td>Osteoclastic abnormality: ↓ bone turnover</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteoclastic abnormality: unclear</td>
<td>Deformities, pain, CHF, fractures</td>
<td>Coarse trabeculae, picture-frame vertebrae</td>
</tr>
</tbody>
</table>

↓, Decreased; ↑, increased.
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>CHANGES IN LEVEL OR CONCENTRATION</th>
<th>OTHER FINDINGS OR POSSIBLE FINDINGS</th>
<th>TREATMENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary hyperparathyroidism</strong></td>
<td>↑</td>
<td>None or ↓</td>
<td>↑ None or ↓</td>
<td>Active turnover observed on bone biopsy with peritrabecular fibrosis Brown tumors Surgical excision of parathyroid edema Treatment of hypercalcemia (see text) Most commonly caused by parathyroid adenoma Because PTH stimulates conversion of the inactive form to the active form ([1,25(OH)_2D]) in the kidney, ↑ production of PTH leads to ↑ levels of ([1,25(OH)_2D]) Calcium levels may lead to ↑ PTH production through feedback mechanism ↑ ([1,25(OH)_2D]) levels result from ↑ PTH (responsible for conversion of inactive to active form of vitamin D in the kidney) Patients with multiple myeloma display abnormal urinary and serum protein electrophoresis ↑ Calcium levels caused by ↑ bone turnover (hypermetabolic state) History of excessive vitamin D intake Dietary vitamin D is converted to ([25(OH)_D]) in the liver; very high concentrations of ([25(OH)_D]) cross-react with intestinal vitamin D receptors to ↓ resorption of calcium and cause hypercalcemia</td>
</tr>
<tr>
<td>Malignancy with bony metastases</td>
<td>↑</td>
<td>None or ↑</td>
<td>None or ↓</td>
<td>Destructive lesions in bone Treatment of cancer and hypercalcemia (see text) ↑ calcium levels may lead to ↑ PTH production through feedback mechanism ↑ ([1,25(OH)_2D]) levels result from ↑ PTH (responsible for conversion of inactive to active form of vitamin D in the kidney)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>↑</td>
<td>None</td>
<td>↑ None or ↓</td>
<td>↑ Free thyroxin index ↑ Thyroid-stimulating hormone Tachycardia, tremors Treatment of hyperthyroidism ↑ calcium levels caused by ↑ bone turnover (hypermetabolic state)</td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
<td>↑</td>
<td>None or ↑</td>
<td>None or ↓</td>
<td>Normalization of vitamin D intake and levels History of excessive vitamin D intake Dietary vitamin D is converted to ([25(OH)_D]) in the liver; very high concentrations of ([25(OH)_D]) cross-react with intestinal vitamin D receptors to ↓ resorption of calcium and cause hypercalcemia</td>
</tr>
</tbody>
</table>

↑, Increased; ↓, Decreased.
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>SERUM CALCIUM</th>
<th>SERUM PHOSPHATASE</th>
<th>ALKALINE PHOSPHATASE</th>
<th>PTH</th>
<th>25(OH)D</th>
<th>1,25(OH)(_2)D</th>
<th>URINARY CALCIUM</th>
<th>OTHER FINDINGS OR POSSIBLE FINDINGS</th>
<th>TREATMENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoparathyroidism</td>
<td>↓</td>
<td>↑</td>
<td>None</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Basal ganglia calcification</td>
<td>Calcium and vitamin D supplementation</td>
<td>↓ PTH production most commonly follows surgical ablation of the thyroid (with the parathyroid) gland</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Hypocalcemic findings</td>
<td></td>
<td>↓ PTH leads to ↓ serum calcium and ↑ serum phosphate (as result of ↓ urinary excretion of phosphate)</td>
</tr>
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<td></td>
<td>Because PTH stimulates conversion from the inactive to the active form of vitamin D (in the kidney), 1,25(OH)(_2)D is also ↓</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>↓</td>
<td>↑</td>
<td>None</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
<td>Calcium and vitamin D supplementation</td>
<td>↓ PTH has no effect on the target cells (in the kidney, bone, and intestine) because of a PTH receptor abnormality</td>
</tr>
<tr>
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<td></td>
<td>Leads to a ↓ in the active form of vitamin D</td>
</tr>
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<td></td>
<td>Therefore, serum calcium levels are ↓ as result of (1) lack of effect of PTH on bone and (2) ↓ levels of 1,25(OH)(_2)D</td>
</tr>
<tr>
<td>Renal osteodystrophy (high-turnover bone disease resulting from renal disease [secondary hyperparathyroidism])</td>
<td>↓ or none</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑</td>
<td>None</td>
<td>Findings of secondary hyperparathyroidism: rugger jersey spine Osteitis fibrosa Amyloidosis</td>
<td>Correction of underlying renal abnormality Maintenance of normal serum phosphorous and calcium Dietary phosphate restriction Phosphate-binding antacid (calcium carbonate) Administration of the active form of vitamin D: 1,25(OH)(_2)D (calcitriol)</td>
<td>↓ Renal phosphorus excretion leads to hyperphosphatemia Phosphorus retention leads to ↓ serum calcium and ↑↑↑ PTH (which can lead to secondary hyperparathyroidism)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>↓ BUN and creatinine levels Associated with long-term hemodialysis</td>
</tr>
<tr>
<td>Renal osteodystrophy (low-turnover bone disease due to renal disease [aluminum toxicity])</td>
<td>↓ or none</td>
<td>None or ↑↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑</td>
<td>None or ↑↑↑</td>
<td>Rugger jersey spine Osteitis fibrosa Amyloidosis Osteomalacia may be observed</td>
<td>Treatment of the urinary obstruction or kidney disease</td>
<td>PTH levels may be suppressed because of (1) frequent episodes of hypercalcemia and (2) direct inhibitory effect of aluminum on PTH No secondary hyperparathyroidism is present</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ BUN and creatinine levels Associated with long-term hemodialysis</td>
</tr>
</tbody>
</table>

↓, Decreased; ↑, increased.
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>SERUM CALCIUM</th>
<th>SERUM PHOS</th>
<th>ALKALINE PHOS</th>
<th>PTH</th>
<th>25(OH)D</th>
<th>1,25(OH)₂D</th>
<th>URINARY CALCIUM</th>
<th>OTHER FINDINGS OR POSSIBLE FINDINGS</th>
<th>TREATMENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional rickets: vitamin D deficiency</td>
<td>↓ or none</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Osteomalacia, hypotonia, Muscle weakness, tetany, Bowing deformities of the long bones, Rachitic rosary</td>
<td>Oral vitamin D (1000–6000 IU/day)</td>
<td>With ↓ vitamin D intake, intestinal calcium and phosphorus absorption is reduced, leading to hypocalcemia</td>
</tr>
<tr>
<td>Nutritional rickets: calcium deficiency</td>
<td>↓ or none</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>None</td>
<td>↓</td>
<td>↓</td>
<td>Clinical findings similar to those for vitamin D deficiency</td>
<td>Oral calcium (1000 mg/day)</td>
<td>↓ Serum calcium stimulates ↑ PTH (secondary hyperparathyroidism), leading to bone resorption and ↓ serum calcium (toward or to normal levels)</td>
</tr>
<tr>
<td>Nutritional rickets: phosphate deficiency</td>
<td>None</td>
<td>↓</td>
<td>↑</td>
<td>None</td>
<td>None</td>
<td>↑</td>
<td>↓</td>
<td>No changes of secondary hyperparathyroidism are observed</td>
<td>Oral supplementation of phosphate</td>
<td>None or ↓ Serum phosphate leads to ↑ renal production of 1,25(OH)₂D</td>
</tr>
<tr>
<td>Hereditary vitamin D-dependent rickets type I (pseudo–vitamin D deficiency)</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>None ↑↓</td>
<td>↑↓</td>
<td>↓</td>
<td>Osteomalacia, Clinical findings similar to (but more severe than) those of nutritional rickets due to vitamin D deficiency</td>
<td>Oral physiologic doses (1–2 µg/day) of 1,25(OH)₂D</td>
<td>There is a defect in renal 25(OH)D ¹α-hydroxylase. This enzymatic defect inhibits conversion from the inactive form [25(OH)D] to the active form [1,25(OH)₂D] of vitamin D in the kidney</td>
</tr>
<tr>
<td>Hereditary vitamin D-dependent rickets type II [hereditary resistance to 1,25(OH)₂D]</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>None ↑↓</td>
<td>↑↓</td>
<td>↓</td>
<td>Osteomalacia, Alopecia, Clinical findings similar to (but more severe than) nutritional rickets caused by vitamin D deficiency</td>
<td>Long-term (3–6 mo) daily administration of high-dose vitamin D analogue [1,25(OH)₂D or (OH)D 1α-hydroxylase] plus 3 g/day of elemental calcium</td>
<td>There is an intracellular receptor defect for 1,25(OH)₂D</td>
</tr>
<tr>
<td>Hypophosphatemic rickets (also known as vitamin D–resistant rickets and phosphate diabetes; Albright syndrome is an example of a hypophosphatemic syndrome)</td>
<td>None</td>
<td>↑↓</td>
<td>↑</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Osteomalacia, No changes of secondary hyperparathyroidism, Classic triad: 1. Hypophosphatemia 2. Lower limb deformities 3. Stunted growth rate</td>
<td>First line treatment with burosumab (anti-FGF23 monoclonal antibody), second line elemental phosphate (1–2 g/day plus vitamin D 0.5–1 µg/day)</td>
<td>There is an inborn error in phosphate transport (probably located in the proximal nephron); this leads to failure of reabsorption of phosphate in the kidney and “spilling” of phosphate (phosphate diabetes) in the urine</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Osteomalacia, Early loss of teeth</td>
<td>There is no established medical therapy</td>
<td>Although the absolute levels of 1,25(OH)₂D are normal, they are inappropriately low with regard to the degree of phosphaturia; production of 1,25(OH)₂D is normally stimulated by ↓ serum phosphorous (see Table 1.12)</td>
</tr>
</tbody>
</table>

1. Decreased; 1. Increased; phos, phosphatase.
<table>
<thead>
<tr>
<th></th>
<th>Calcium Level</th>
<th>Phosphorus Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>Hypoparathyroidism</td>
<td>Malignancy with bony metastasis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Pseudohypoparathyroidism</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
<td>Renal osteodystrophy (high-turnover bone disease)</td>
<td>Nutritional rickets: vitamin D deficiency</td>
</tr>
<tr>
<td>Malignancy without bony metastasis</td>
<td>Nutritional rickets: calcium deficiency</td>
<td>Malignancy with bony metastasis</td>
</tr>
<tr>
<td>Malignancy with bony metastasis</td>
<td>Hereditary vitamin D–dependent rickets (types I and II)</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Malignancy with bony metastasis</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Multiple myeloma</td>
<td>Vitamin D intoxication</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>Multiple myeloma</td>
<td>Renal osteodystrophy (only low-turnover bone disease)</td>
</tr>
<tr>
<td>Milk-alkali syndrome</td>
<td>Multiple myeloma</td>
<td>Hypophosphatemic rickets</td>
</tr>
<tr>
<td>Severe generalized immobiliarization</td>
<td>Multiple myeloma</td>
<td>Hypophosphatemic rickets</td>
</tr>
<tr>
<td>Multiple endocrine neoplasias</td>
<td>Multiple myeloma</td>
<td>Hypophosphatemic rickets</td>
</tr>
<tr>
<td>Addison disease</td>
<td>Multiple myeloma</td>
<td>Renal osteodystrophy</td>
</tr>
<tr>
<td>Steroid administration</td>
<td>Multiple myeloma</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>Multiple myeloma</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>Multiple myeloma</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Multiple myeloma</td>
<td>Multiple myeloma</td>
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<td>Nutritional rickets: calcium deficiency</td>
<td>Multiple myeloma</td>
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</tr>
<tr>
<td>Hereditary vitamin D–dependent rickets (types I and II)</td>
<td>Multiple myeloma</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td><strong>Decreased</strong></td>
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</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Osteoporosis</td>
<td>Malignancy with bony metastasis</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Pseudohypoparathyroidism</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Renal osteodystrophy</td>
<td>Nutritional rickets: vitamin D deficiency</td>
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<tr>
<td>(high-turnover bone disease)</td>
<td>Nutritional rickets: calcium deficiency</td>
<td>Malignancy with bony metastasis</td>
</tr>
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<td>Nutritional rickets: calcium deficiency</td>
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<td>Multiple myeloma</td>
</tr>
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<td>Renal osteodystrophy (only low-turnover bone disease)</td>
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<tr>
<td>Nutritional rickets: phosphate deficiency</td>
<td>Hypophosphatemic rickets</td>
<td>Hereditary vitamin D–dependent rickets (types I and II)</td>
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<td>Hypophosphatemic rickets</td>
<td>Hypophosphatemic rickets</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
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<tr>
<td>Primary hyperparathyroidism</td>
<td>Osteoporosis</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Malignancy without bony metastasis</td>
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<td>Multiple myeloma</td>
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<td>Nutritional rickets: phosphate deficiency</td>
<td>Hypophosphatemic rickets</td>
<td>Hypophosphatemic rickets</td>
</tr>
</tbody>
</table>
- Familial hypocalciuric hypercalcemia
- Poor renal clearance of calcium
- Malignancy (most common)
  - Can be life threatening, commonly associated with muscle weakness
  - Initial treatment should include hydration with normal saline (reverses dehydration).
  - Can occur in the absence of extensive bone metastasis
  - Most commonly results from release of systemic growth factors and cytokines that stimulate osteoclastic bone resorption at bony sites not involved in the tumor process (RANKL pathway)
  - PTH-related protein secretion (lung carcinoma)
  - Lytic bone metastases and lesions (e.g., multiple myeloma)
- Hyperthyroidism
- Vitamin D intoxication
- Prolonged immobilization
- Steroid administration
- Peptic ulcer disease (milk-alkali syndrome)
- Kidney disease
- Sarcoidosis
- Hypophosphatasia
- Treatment of hypercalcemia
  - Hydration (saline diuresis)
  - Loop diuretics
  - Dialysis (for severe cases)
  - Mobilization (prevents further bone resorption)
  - Specific drugs (bisphosphonates, mithramycin, calcitonin, and gallium nitrate)

### Hypocalcemia (Fig. 1.17)
- Findings
  - Low plasma calcium
  - Results from low levels of PTH or vitamin D$_3$
  - Neuromuscular irritability (tetany, seizures, Chvostek sign), cataracts, fungal nail infections, ECG changes (prolonged QT interval), and other signs and symptoms

### Hypoparathyroidism
- Reduced PTH level causes decrease in plasma calcium level and increase in plasma phosphate level
- Urinary excretion not enhanced because of the lack of PTH
- Common findings:
  - Fungal nail infections
  - Hair loss
  - Blotchy skin (pigment loss, vitiligo)
  - Skull radiographs may show basal ganglia calcification.
- Iatrogenic hypoparathyroidism most commonly follows thyroidectomy.

### Pseudohypoparathyroidism (PHP)
- A rare genetic disorder caused by lack of effect of PTH on the target cells
- PTH is normal or high.
- PTH action is blocked by an abnormality at the receptor, by the cAMP system, or by a lack of required cofactors (e.g., Mg$^{2+}$)
- Defect in GNAS gene from mother
- Albright hereditary osteodystrophy, a form of PHP
  - Short first, fourth, and fifth metacarpals (MCs) and metatarsals (MTs)
  - Brachydactyly
  - Exostoses
  - Obesity
  - Diminished intelligence

### Pseudo-pseudohypoparathyroidism (pseudo-PHP)
- Normocalcemic disorder that is phenotypically similar to PHP
- However, response to PTH is normal.
- Renal osteodystrophy (Fig. 1.18)
  - A spectrum of bone mineral metabolism disorders in chronic renal disease.
  - Due to impaired excretion, which compromises mineral homeostasis
  - Leads to abnormalities in bone mineral metabolism
  - High-turnover renal bone disease
    - Chronically elevated serum PTH level leads to secondary hyperparathyroidism (hyperplasia of parathyroid gland chief cells).
    - Factors contributing to sustained PTH increase and secondary hyperparathyroidism include:
      - Diminished renal phosphorus excretion; phosphorus retention promotes PTH secretion by three mechanisms:
        - Hyperphosphatemia lowers serum calcium, stimulating PTH.
        - Phosphorus impairs renal 1α-hydroxylase activity, impairing production of 1,25(OH)$_2$D$_3$.
        - Phosphorus retention may directly increase the synthesis of PTH.
• Hypocalcemia
• Impaired renal calcitriol (1,25(OH)₂D₃)
• Alterations in the control of PTH gene transcription secretion
• Skeletal resistance to the actions of PTH
• Low-turnover renal bone disease (adynamic lesion of bone and osteomalacia)
• Secondary hyperparathyroidism is not characteristic with this condition.
• Serum PTH level is normal or mildly elevated.
• Bone formation and turnover are reduced.
• Excess deposition of aluminum into bone (aluminum toxicity) negatively affects bone mineral metabolism.
• Impairs differentiation of precursor cells to osteoblasts
• Impairs proliferation of osteoblasts
• Impairs PTH release from the parathyroid gland
• Disrupts the mineralization process
• Adynamic lesion: accounts for the majority of cases of low-turnover bone disease in patients with chronic renal failure
• Osteomalacia: defects in mineralization of newly formed bone
• Radiographs may demonstrate a rugger jersey spine (vertebral bodies appear to have increased density in the upper and lower zones in a striated appearance, like that in childhood osteopetrosis) and soft tissue calcification.
• β₂-Microglobulin may accumulate with long-term dialysis, leading to amyloidosis.
• Amyloidosis may be associated with carpal tunnel syndrome, arthropathy, and pathologic fractures.

• In amyloidosis, Congo red stain causes tissue material to turn pink.
• Laboratory findings:
  • Abnormal glomerular filtration rate (GFR)
  • Increased alkaline phosphatase, blood urea nitrogen (BUN), and creatinine levels
  • Decreased venous bicarbonate level
• Treatment directed at relieving the urologic obstruction or kidney disease
• Rickets (osteomalacia in adults; Box 1.1)
• Failure of mineralization leading to changes in the physis in the zone of provisional calcification (increased width and disorientation) and bone (cortical thinning, bowing)

### Box 1.1 Causes of Rickets and Osteomalacia

#### NUTRITIONAL DEFICIENCY
- Vitamin D deficiency
- Dietary chelators (rare) of calcium
- Phytates
- Oxalates (spinach)

#### PHOSPHORUS DEFICIENCY (UNUSUAL)
- Abuse of antacids (which contain aluminum), which leads to severe dietary phosphate binding

#### GASTROINTESTINAL ABSORPTION DEFECTS
- Postgastrectomy (rare today)
- Biliary disease (interference with absorption of fat-soluble vitamin D)
- Enteric absorption defects
- Short bowel syndrome
- Rapid transit (gluten-sensitive enteropathy) syndromes
- Inflammatory bowel disease
- Crohn disease
- Celiac disease

#### RENAL TUBULAR DEFECTS (RENAL PHOSPHATE LEAK)
- X-linked dominant hypophosphatemic vitamin D–resistant rickets or osteomalacia
- Classic Albright syndrome or Fanconi syndrome type I
- Fanconi syndrome type II
- Phosphaturia and glycosuria
- Fanconi syndrome type III
- Phosphaturia, glycosuria, aminoaciduria
- Vitamin D–dependent rickets (or osteomalacia) type I—a genetic or acquired deficiency of renal tubular 25(OH)D 1α-hydroxylase enzyme that prevents conversion of 25(OH)D to the active polar metabolite 1,25(OH)₂D.
- Vitamin D–dependent rickets (or osteomalacia) type II—which represents enteric end-organ insensitivity to 1,25(OH)₂D and is probably caused by an abnormality in the 1,25(OH)₂D nuclear receptor
- Renal tubular acidosis
- Acquired: associated with many systemic diseases
- Genetic
  - Debré–De Toni–Fanconi syndrome
  - Lignac–Fanconi syndrome (cystinosis)
  - Lowe syndrome

#### RENAL OSTEODYSTROPHY: MISCELLANEOUS CAUSES
- Soft tissue tumors secreting putative factors
  - Fibrous dysplasia
  - Neurofibromatosis
- Other soft tissue and vascular mesenchymal tumors
- Anticonvulsant medication (induction of the hepatic P450 microsomal enzyme system by some anticonvulsants—e.g., phenytoin, phenobarbital, and primidone [Mysoline]—causes increased degradation of vitamin D metabolites)
- Heavy metal intoxication
- Hypophosphatasia
- High-dose diphosphonates
- Sodium fluoride

---

**FIG. 1.18** Pathogenesis of bony changes in renal osteodystrophy. PTHR, proximal tubule reabsorption. (From McPherson RA, Pincus MR, editors: **Henry’s clinical diagnosis and management by laboratory methods**, ed 21, Philadelphia, 2007, Saunders Elsevier.)

- Nutritional rickets (see Table 1.16)
  - Vitamin D–deficiency rickets
    - Rare after addition of vitamin D to milk, except in the following populations:
      - Asian immigrants
      - Patients with dietary peculiarities
      - Premature infants
      - Patients with malabsorption (celiac sprue)
      - Patients receiving long-term parenteral nutrition
    - Decreased intestinal absorption of calcium and phosphate leads to secondary hyperparathyroidism.
  - Laboratory findings
    - Low-normal calcium level (maintained by high PTH level)
    - Low phosphate level (excreted because of the effect of PTH)
    - Increased alkaline phosphatase level
    - Low vitamin D level
    - Increased PTH level leads to higher bone absorption
  - Physical examination
    - Enlargement of the costochondral junction (rachitic rosary)
    - Bowing of the knees
    - Muscle hypotonia
    - Dental disease
    - Pathologic fractures (Looser zones: pseudo-fractures on the compression sides of bones)
    - Milkman’s fracture
  - Waddling gait
  - Radiographic findings
  - Physeal widening and cupping
  - Coxa vara
  - Codfish vertebrae
  - Retarded bone growth (defect in the hypertrophic zone, widened osteoid seams)
  - In affected children, height is commonly below the fifth percentile for age.
  - Treatment with vitamin D (1000–6000 IU daily based on weight) resolves most deformities.
  - Calcium-deficiency rickets (Fig. 1.19)
  - Phosphate-deficiency rickets
  - Hereditary vitamin D–dependent rickets
    - Rare disorders with features similar to those of vitamin D–deficiency (nutritional) rickets, except that symptoms may be worse and patients may have total baldness
      - Type I: defect in renal 25(OH)D 1α-hydroxylase, inhibiting conversion of inactive vitamin D to its active form
        - Autosomal recessive inheritance
        - Gene on chromosome 12q14
      - Type II: defect in an intracellular receptor for 1,25(OH)2D3
        - Familial hypophosphatemic rickets (vitamin D–resistant rickets or phosphate diabetes)
        - Most commonly encountered form of rickets
        - X-linked dominant inheritance

**FIG. 1.19** Nutritional calcium deficiency. (From Netter FH: CIBA collection of medical illustrations, vol 8: Musculoskeletal system, part I: Anatomy, physiology and developmental disorders, Basel, Switzerland, 1987, CIBA, p 184.)
• Impaired renal tubular reabsorption of phosphate
• Normal GFR with an impaired vitamin D₃ response
• Normal serum calcium, low serum phosphorus and 1, (OH)₂D₃, and high serum alkaline phosphatase levels

Treatment:
• First line treatment with burosumab (anti-FGF23 monoclonal antibody)
• Second line elemental phosphate (1–2 g/day plus vitamin D 0.5–1 µg/day)

- Hypophosphatasia
  - Autosomal recessive
  - Error in the tissue-nonspecific isoenzyme of alkaline phosphatase
  - Leads to low levels of alkaline phosphatase, which is required for synthesis of inorganic phosphate (Pi) and important in bone matrix formation
  - Features are similar to those of rickets.
  - Increased urinary phosphoethanolamine is diagnostic.
  - Treatment may include phosphate therapy.

**Conditions of bone mineral density**

- Bone mass is regulated by rates of deposition and withdrawal (Fig. 1.20).

- Osteoporosis
  - Age-related decrease in bone mass
    - Usually associated with estrogen loss in postmenopausal women (Fig. 1.21)
    - A quantitative, not qualitative, defect
    - Mineralization remains normal
  - World Health Organization’s definition
    - Lumbar (L2–L4) density is 2.5 or more standard deviations less than mean peak bone mass of a healthy 25-year-old (T-score).
    - Osteopenia: bone density is 1.0–2.5 standard deviations less than the mean peak bone mass of a healthy 25-year-old.
  - Responsible for more than 1 million fractures per year
  - Fractures of the vertebral body are most common.
  - History of osteoporotic vertebral compression fractures are strongly predictive of subsequent vertebral fracture.
    - After initial vertebral fracture, the risk for a second vertebral fracture is 20%.
  - Vertebral compression fracture is associated with increased mortality rate.
    - Incidence of vertebral compression fractures is higher among men than women.
  - Lifetime risk of fracture in white women after 50 years of age: 75%
  - The risk for hip fracture is 15%–20%.

- Risk factors (Box 1.2)
  - Cancellous bone is most affected.
  - Clinical features
    - Kyphosis and vertebral fractures
      - Compression fractures of T11–L1 that create anterior wedge-shaped defects or centrally depressed codfish vertebrae
    - Hip fractures
    - Distal radius fractures
  - Type I osteoporosis (postmenopausal)
    - Primarily affects trabecular bone
    - Vertebral and distal radius fractures common
  - Type II osteoporosis (age-related)
    - Patients older than 75 years
    - Affects both trabecular and cortical bone

- Related to poor calcium absorption
- Hip and pelvic fractures are common.

- Laboratory studies
  - Obtained to rule out secondary causes of low bone mass:
    - Vitamin D deficiency, hyperthyroidism, hyperparathyroidism, Cushing syndrome, hematologic disorders, malignancy
  - Complete blood cell count; measurements of serum calcium, phosphorus, 25(OH)D, alkaline phosphatase, liver enzymes, creatinine, and total protein and albumin levels; and measurement of 24-hour urinary calcium excretion
  - Results of these studies are usually unremarkable in osteoporosis.
  - Plain radiographs not helpful unless bone loss exceeds 30%

- Special studies
  - Single-photon (appendicular) absorptiometry
  - Double-photon (axial) absorptiometry
  - Quantitative computed tomography (CT)
  - Dual-energy x-ray absorptiometry (DEXA)
    - Most accurate with less radiation

- Biopsy
  - After tetracycline labeling
  - To evaluate the severity of osteoporosis and identify osteomalacia

- Histologic changes
  - Thinning trabeculae
  - Decreased osteon size
  - Enlarged haversian and marrow spaces

- Treatment (Fig. 1.22)
  - Physical activity
  - Supplements: 1000–1500 mg calcium plus 400–800 IU of vitamin D per day
    - More effective in type II (age-related) osteoporosis
  - Bisphosphonates
    - Inhibit osteoclastic bone resorption—direct anabolic effect on bone
    - Categorized into two classes on the basis of the presence or absence of a nitrogen side group:
      - Nitrogen-containing bisphosphonates—up to 1000-fold more potent in their antiresorptive activity
        - Zoledronic acid (Zometa) and alendronate (Fosamax)
        - Inhibit protein prenylation within the mevalonate pathway, blocking farnesyl pyrophosphate synthase
      - Results in a loss of GTPase formation, which is needed for ruffled border formation and cell survival
        - Non–nitrogen-containing bisphosphonates
          - Metabolized into a nonfunctional ATP analogue, inducing apoptosis
          - Decreases skeletal events in multiple myeloma
        - Associated with osteonecrosis of the jaw
      - Orthopaedic implications of bisphosphonate use
        - Spine—reduced rate of spinal fusion in animal model; withholding bisphosphonate is recommended after surgery.
        - Hip and knee—safe for use in cementless hip arthroplasty and cemented knee arthroplasty; may decrease rate of acetabular component subsidence
Fracture healing—no good data to recommend for or against use; will decrease future fracture risk.

Denosumab is a monoclonal antibody that targets and inhibits RANKL binding to the RANK receptor, which is found on osteoclasts.

Other drugs (e.g., intramuscular calcitonin) may be helpful.

Expensive and may cause hypersensitivity reactions.

Efficacy of bone augmentation with PTH, growth factors, prostaglandin inhibitors, and other therapies remains to be determined.

Prophylaxis for patients at risk for osteoporosis

Diet with adequate calcium intake

Weight-bearing exercise program
Estrogen therapy evaluation at menopause

Other causes of decreased mineral density

Idiopathic transient osteoporosis of the hip

Uncommon; diagnosis of exclusion

Most common during third trimester of pregnancy in women but can occur in men

Groin pain, limited ROM, and localized osteopenia without a history of trauma

Treatment: analgesics and limited weight bearing

Generally self-limiting and tends to resolve spontaneously after 6–8 months

Stress fractures may occur.

Joint space remains preserved on radiographs.

Osteomalacia

Femoral neck fractures are common.

Qualitative defect

Defect of mineralization results in a large amount of unmineralized osteoid.

Causes:

Vitamin D–deficient diet

GI disorders

Renal osteodystrophy

Certain drugs

Aluminum-containing phosphate-binding antacids; aluminum deposition in bone prevents mineralization

Phenytoin (Dilantin)

Osteoporosis and osteomalacia are compared in Fig. 1.23.

 box 1.2 Risk Factors for the Development of Osteoporosis

- White race, female gender, northern European descent (fair skin and hair)
- Sedentary lifestyle
- Thinness
- Smoking
- Heavy drinking
- Phenytoin (impairs vitamin D metabolism)
- Diet low in calcium and vitamin D
- History of breastfeeding
- Positive family history of osteoporosis
- Premature menopause


- Estrogen therapy evaluation at menopause

- Other causes of decreased mineral density

- Idiopathic transient osteoporosis of the hip

- Uncommon; diagnosis of exclusion

- Most common during third trimester of pregnancy in women but can occur in men

- Groin pain, limited ROM, and localized osteopenia without a history of trauma

- Treatment: analgesics and limited weight bearing

- Generally self-limiting and tends to resolve spontaneously after 6–8 months

- Stress fractures may occur.

- Joint space remains preserved on radiographs.

- Osteomalacia

- Femoral neck fractures are common.

- Qualitative defect

- Defect of mineralization results in a large amount of unmineralized osteoid.

- Causes:

  - Vitamin D–deficient diet
  - GI disorders
  - Renal osteodystrophy
  - Certain drugs

  - Aluminum-containing phosphate-binding antacids; aluminum deposition in bone prevents mineralization
  - Phenytoin (Dilantin)

- Alcoholism

- Radiographic findings

  - Looser zones (microscopic stress fractures)
  - Other fractures

  - Biconcave vertebral bodies

  - Trefoil pelvis

  - Biopsy (transiliac) required for diagnosis

  - Widened osteoid seams are histologic findings.

- Treatment: usually includes large doses of vitamin D

- Scurvy

  - Vitamin C (ascorbic acid) deficiency

  - Produces a decrease in chondroitin sulfate synthesis

  - Leads to defective collagen growth and repair
Comparison of Osteoporosis and Osteomalacia

**Definition**

- **Osteoporosis**: Bone mass decreased, mineralization normal
- **Osteomalacia**: Bone mass variable, mineralization decreased

**Age at onset**

- **Osteoporosis**: Generally in old age, after menopause
- **Osteomalacia**: Any age

**Etiology**

- **Osteoporosis**: Endocrine abnormality, age, idiopathic cause, inactivity, disuse, alcoholism, calcium deficiency
- **Osteomalacia**: Vitamin D deficiency, abnormality of vitamin D pathway, hypophosphatemic syndromes, renal tubular acidosis, hypophosphatasia

**Symptoms**

- **Osteoporosis**: Pain referable to fracture site
- **Osteomalacia**: Generalized bone pain

**Signs**

- **Osteoporosis**: Tenderness at fracture site
- **Osteomalacia**: Tenderness at fracture site and generalized tenderness

**Radiographic features**

- **Osteoporosis**: Axial predominance
- **Osteomalacia**: Appendicular predominance

**Laboratory findings**

<table>
<thead>
<tr>
<th></th>
<th>Osteoporosis</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca²⁺</td>
<td>Normal</td>
<td>Low or normal (high in hypophosphatasia)</td>
</tr>
<tr>
<td>Serum P,</td>
<td>Normal</td>
<td>Low or normal (high in hypophosphatasia)</td>
</tr>
<tr>
<td>Ca²⁺ x P, &gt;30</td>
<td></td>
<td>Ca²⁺ x P, &gt;30 if albumin normal (high in renal osteodystrophy)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Normal</td>
<td>Elevated, except in hypophosphatasia</td>
</tr>
<tr>
<td>Urinary Ca²⁺</td>
<td>High or normal</td>
<td>Normal or low (high in hypophosphatasia)</td>
</tr>
<tr>
<td>Bone biopsy</td>
<td>Tetracycline labels normal</td>
<td>Tetracycline labels abnormal</td>
</tr>
</tbody>
</table>

*FIG. 1.23* Comparison of osteoporosis and osteomalacia. (From Netter FH: CIBA collection of medical illustrations, vol 8: Musculoskeletal system, part I: Anatomy, physiology and developmental disorders, Basel, Switzerland, 1987, CIBA, p 228.)
• Also leads to impaired intracellular hydroxylation of collagen peptides
• Clinical features:
  • Fatigue
  • Gum bleeding
  • Ecchymosis
  • Joint effusions
  • Iron deficiency
• Radiographic findings:
  • May include thin cortices and trabeculae and metaphyseal clefts (corner sign)
• Laboratory studies: normal results
• Histologic features
  • Primary trabeculae replaced with granulation tissue
  • Areas of hemorrhage
  • Widening of the zone of provisional calcification in the physis
    • Greatest effect on bone formation in the metaphysis
• Marrow packing disorders
  • Myeloma, leukemia, and other such disorders can cause osteopenia.
• Lead poisoning
  • Results in short stature and reduced bone density
  • Lead alters the chondrocyte response to PTH-related protein and TGF-β.

Increased osteodensity
• Osteopetrosis (marble bone disease)
  • Result of decreased osteoclast (and chondroclast) function: failure of bone resorption
• Osteopokilosis (spotted bone disease)
  • Islands of deep cortical bone appear within the medullary cavity and the cancellous bone of the long bones
    • Especially in the hands and feet
    • These areas are usually asymptomatic
  • This disease is accompanied by no known incidence of malignant degeneration.
• Paget disease of bone (osteitis deformans)
  • Elevated serum alkaline phosphatase and urinary hydroxyproline levels
• Virus-like inclusion bodies in osteoclasts—abnormal function of osteoclasts
  • Both decreased and increased osteodensities may be present.
    • Depends on phase of disease
      • Active phase
        • Lytic phase: intense osteoclastic bone resorption
        • Mixed phase
          • Sclerotic phase: osteoblastic bone formation
          • Inactive phase

Conditions of bone viability
Osteonecrosis
• Death of bony tissue from causes other than infection
  • Usually adjacent to a joint surface
  • Caused by loss of blood supply as a result of trauma or another event (e.g., SCFE)
  • Idiopathic osteonecrosis of the femoral head and Legg-Calvé-Perthes disease may occur in patients with coagulation abnormalities.
  • Deficiency of antithrombin factors protein C and protein S
  • Increased levels of lipoprotein(a)
  • Commonly affects the hip joint
  • Leads to collapse and flattening of the femoral head, most frequently the anterolateral region

Associated with the following conditions:
• Steroids
• Heavy alcohol use
• Blood dyscrasias (e.g., sickle cell disease)
• Dysbarism (caisson disease)
• Excessive radiation therapy
• Gaucher disease
• Cause
  • Osteonecrosis may be related to enlargement of space-occupying marrow fat cells, which lead to ischemia of adjacent tissues.
  • Vascular insults and other factors may also be significant.
  • Idiopathic (or spontaneous) osteonecrosis is diagnosed when no other cause can be identified.
  • Chandler disease: osteonecrosis of the femoral head in adults
  • Medial femoral condyle osteonecrosis: most common in women older than 60 years
    • Idiopathic, alcohol, and dysbaric forms of osteonecrosis are associated with multiple insults.
    • These may be secondary to a hemoglobinopathy (e.g., sickle cell disease) or marrow disorder (e.g., hemochromatosis).
  • Cyclosporine has reduced the incidence of osteonecrosis of the femoral head among renal transplant recipients.
  • Pathologic changes
    • Grossly necrotic bone, fibrous tissue, and subchondral collapse (Figs. 1.24 and 1.25)
  • Histologic findings
    • Early changes (14–21 days) involve autolysis of osteocytes and necrotic marrow.
    • Followed by inflammation with invasion of buds of primitive mesenchymal tissue and capillaries
    • Newly woven bone is laid down on top of dead trabecular bone.

![FIG. 1.24 Fine-grain micrograph demonstrating space between articular surface and subchondral bone: crescent sign of osteonecrosis. (From Steinberg ME: The hip and its disorders, Philadelphia, 1991, Saunders, p 630.)](image-url)
Followed by resorption of dead trabeculae and remodeling through creeping substitution
The bone is weakest during resorption and remodeling.
Collapse (crescent sign on radiographs) and fragmentation can occur.
Evaluation
A careful history (to discern risk factors) and physical examination (e.g., to discern decreased ROM, limp) should precede additional studies.
Other joints (especially the contralateral hip) should be evaluated to identify the disease process early.
The process is bilateral in the hip in 50% of cases of idiopathic osteonecrosis and up to 80% of cases of steroid-induced osteonecrosis.
MRI and bone scanning are helpful for early diagnosis.
MRI: earliest study to yield positive results; highest sensitivity and specificity
Treatment
Resurfacing arthroplasty of the hip is associated with increased risk of implant loosening and failure.
Total hip arthroplasty is indicated in Ficat stage III or IV.
Nontraumatic osteonecrosis of the distal femoral condyle and proximal humerus may improve spontaneously without surgery.
Precise role of core decompression remains unresolved.
Results are best when core decompression is performed in early hip disease (Ficat stage I).
Osteochondrosis (Table 1.18)
Can occur at traction apophyses in children
May or may not be associated with trauma, joint capsule inflammation, vascular insult, or secondary thrombosis

CARTILAGE AND JOINT

- **Hyaline cartilage characteristics**
- **Articular bearing surface**
- Decreases friction and distributes loads
- Coefficient of friction in healthy human joint is less than that of ice on ice (0.002–0.04).
- Shock-absorbing cushion resists shear/compression.
- Withstands impact loads up to 25 N/mm²
- Avascular, aneural, and alymphatic
- Receives nutrients and oxygen from synovial fluid via diffusion
- Heals poorly
- Anisotropic: Properties vary with direction of force
- **Viscoelastic:** Properties vary according to rate of force application.
- Biphasic—property of liquid and solid
- Cartilage homeostasis disrupted by:
  - Direct trauma/excess or inadequate forces
  - Loss of underlying bone structure
  - Genetic defects in normal structure/function
  - Chemical/enzymatic threats

**Hyaline cartilage composition**

- **Water**
  - Approximately 75% of cartilage
  - Highest at surface or superficial layers
  - Recurrent low-level forces shifts water in and out of extracellular matrix (ECM)
  - Responsible for nutrition and lubrication
  - H₂O decreases with aging
  - H₂O increases in osteoarthritis (Fig. 1.26)

- **Collagen**
  - Makes up approximately 15% of wet weight (60% of dry weight) (Fig. 1.27; Table 1.19)
  - **Type II collagen: 90%–95% of collagen**
    - Triple helix of α chains (derived from COL2A1 gene)
    - Genetic defects of type II cause achondrogenesis (lethal at birth), spondyloepiphyseal dysplasia congenita, precocious arthritis
  - Types IX and XI are “linking collagens”
  - **Type X found only near calcified cartilage, including:**
    - Calcified zone of articular cartilage’s tidemark
    - Hypertrophic zone of the physis (genetic defect of type X leads to Schmid metaphyseal chondrodysplasia)
    - Fracture callus and calcifying cartilaginous tumors
  - Provides shear and tensile strength

**Table 1.18 Common Types of Osteochondrosis**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>SITE</th>
<th>AGE (YR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Neck disease</td>
<td>Ischiopubic synchondrosis</td>
<td>4–11</td>
</tr>
<tr>
<td>Legg-Calvé-Perthes disease</td>
<td>Femoral head</td>
<td>4–8</td>
</tr>
<tr>
<td>Osgood-Schlatter disease</td>
<td>Tibial tuberosity</td>
<td>11–15</td>
</tr>
<tr>
<td>Sinding-Larsen-Johansson syndrome</td>
<td>Inferior patella</td>
<td>10–14</td>
</tr>
<tr>
<td>Blount disease in infants</td>
<td>Proximal tibial epiphysis</td>
<td>1–3</td>
</tr>
<tr>
<td>Blount disease in adolescents</td>
<td>Proximal tibial epiphysis</td>
<td>8–15</td>
</tr>
<tr>
<td>Sever disease</td>
<td>Calcaneus</td>
<td>9–11</td>
</tr>
<tr>
<td>Kölher disease</td>
<td>Tarsal navicular</td>
<td>3–7</td>
</tr>
<tr>
<td>Freiberg infarction</td>
<td>Metatarsal head</td>
<td>13–18</td>
</tr>
<tr>
<td>Scheuermann disease</td>
<td>Discovertebral junction</td>
<td>13–17</td>
</tr>
<tr>
<td>Panner disease</td>
<td>Capitellum of humerus</td>
<td>5–10</td>
</tr>
<tr>
<td>Thiemann disease</td>
<td>Phalanges of hand</td>
<td>11–19</td>
</tr>
<tr>
<td>Kienböck disease</td>
<td>Carpal lunate</td>
<td>20–40</td>
</tr>
</tbody>
</table>
Proteoglycan is an extracellular macromolecule constructed of a protein core that binds with hyaluronan, collagen, and water to form a hydrated matrix of articular cartilage, yielding both lubricant and support functions.

FIG. 1.26 Articular cartilage changes in osteoarthritis and aging. Arrows indicate an increase (when pointing up) or a decrease (when pointing down). (From Brinker MR, Miller MD: Fundamentals of orthopaedics, Philadelphia, 1999, Saunders, p 9.)
FIG. 1.27 Macrostructure to microstructure of collagen. Although the majority of the collagen in bone, tendon, and ligament is type I, most of the collagen in cartilage is type II. Collagen is composed of microfibrils that are quarter-staggered arrangements of tropocollagen. Note the hole and pore regions for mineral deposition (for calcification). Vitamin C (ascorbic acid) is an enzymatic cofactor needed to form the hydroxylated version of the amino acids proline and lysine, which allow the twists to form the triple helix from the polypeptide α chains. EM, Electron microscopy. (Modified from Brinker MR, Miller MD: Fundamentals of orthopaedics, Philadelphia, 1999, Saunders.)

Table 1.19 Collagen Types, Locations, and Related Genetic Disorders

<table>
<thead>
<tr>
<th>TYPE</th>
<th>LOCATION</th>
<th>GENETIC DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Bone, tendon, meniscus</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td></td>
<td>Disc annulus, eye (sclera), skin</td>
<td>Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>II</td>
<td>Articular cartilage</td>
<td>Achondrogenesis (lethal)</td>
</tr>
<tr>
<td></td>
<td>Disc nucleus pulposus, eye (vitreous humor)</td>
<td>Hyprocandrogenesis</td>
</tr>
<tr>
<td></td>
<td>Disc nucleus</td>
<td>Spondyloepiphyseal dysplasia congenita</td>
</tr>
<tr>
<td></td>
<td>Articular cartilage</td>
<td>Kniest dysplasia</td>
</tr>
<tr>
<td>V</td>
<td>Articular cartilage (in small amounts); tethers chondrocyte to pericellular matrix</td>
<td>Stickler syndrome</td>
</tr>
<tr>
<td>VI</td>
<td>Articular cartilage (in small amounts); tethers chondrocyte to pericellular matrix</td>
<td>Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>VII</td>
<td>Basal lamina</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td>VIII</td>
<td>Basement membrane (epithelial)</td>
<td>Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>IX</td>
<td>Articular cartilage (in small amounts); tethers chondrocyte to pericellular matrix</td>
<td>Bethlem myopathy</td>
</tr>
<tr>
<td>X</td>
<td>Hypertrophic zone or tidemark of cartilage (associated with calcified cartilage)</td>
<td>Ulrich congenital muscular dystrophy</td>
</tr>
<tr>
<td>XI</td>
<td>Articular cartilage (in small amounts); acts as an adhesive</td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td>XII</td>
<td>Tendon</td>
<td>Corneal endothelial dystrophy</td>
</tr>
<tr>
<td>XIII</td>
<td>Endothelial cells</td>
<td><strong>Multiple epiphyseal dysplasia</strong> (one type)</td>
</tr>
</tbody>
</table>

*More common orthopaedic diseases are in **bold**.
• Contributes to viscoelastic behavior in that it restrains “swelling” of aggrecan

■ Proteoglycans
  • Make up approximately 10% of wet weight (30% of dry weight) (Fig. 1.28).
  • Half-life of 3 months
  • Provide compression strength
  • Responsible for cartilage's porous structure
  • Trap and hold water
  • Produced by chondrocytes
  • Most common is aggrecan.
    • Large macromolecules shaped like bristle brushes (see Fig. 1.28)
    • Composed of repeating disaccharide subunits or glycosaminoglycans attached to protein core
    • Repeating carboxyl and sulfate groups which are ionized in solution to COO\(^{-}\) and SO\(_3\)^{-}
    • Repel each other but attract positive cations
    • Increase osmotic pressure, which traps and holds water and is responsible for ECM's hydrophilic behavior
    • Provides turgor of matrix
    • Chondroitin sulfate (most prevalent glycosaminoglycan in cartilage)
      • Chondroitin 4-sulfate decreases with age
      • Chondroitin 6-sulfate remains constant
    • Keratin sulfate
      • Increases with age.
    • Multiple core proteins in turn attached to hyaluronic acid (through link proteins) producing proteoglycan aggregate

■ Chondrocytes
  • 1%–5% of wet weight
  • Only cells in cartilage
  • Derived from undifferentiated mesenchymal precursors
  • BMP-2 and the transcriptional factor SOX-9 important in regulating chondrocyte differentiation and formation
  • Mechanotransduction—metabolism modulated via mechanical stimulation
    • Cyclical loads of walking stimulate chondrocytes to form matrix
    • Low loads (1–5 MPa) at moderate frequency (≈1 Hz)
  • Primary cilia are the mechanosensory organ “antennae” for cells.
  • Produce the extracellular matrix of collagen and proteoglycans
    • Intracellular synthesis of procollagen, link peptide, hyaluronic acid, proteoglycans
    • Extracellular assembly of component parts
  • Produce proteins and enzymes and maintain matrix
    • IL-1β (also from synovium and WBCs): main cartilage destroyer
    • Metalloproteinases—break down cartilage matrix
      • Collagenase—dissolves collagen (matrix metalloproteinase 13 [MMP-13])
      • Aggrecanase—degrades proteoglycans (extracellular protease enzyme ADAMT)
    • Enzyme inhibitors—protect cartilage
      • Tissue inhibitors of metalloproteinases (TIMPs)
      • Plasminogen activator inhibitor-1 (PAI-1)
  • Chondrocytes are most dense and most active in the superficial zone.
  • Deeper cartilage zone chondrocytes less metabolically active
    • Decreased rough endoplasmic reticulum
    • Increased intraplasmic filaments (degenerative products)

■ Other matrix components
  • Nonaggregating proteoglycans

---

**FIG. 1.28** Proteoglycan aggregate and bristle brush–shaped aggrecan molecule. Sulfate ions are transmitted by DTDST protein; a defect in the DTDST gene causes diastrophic dysplasia (short stature with hitchhiker’s thumbs and cauliflower ears). (Modified from Brinker MR, Miller MD: Fundamentals of orthopaedics, Philadelphia, 1999, Saunders, p 9.)
Cartilage layers

<table>
<thead>
<tr>
<th>Layer</th>
<th>Width (µm)</th>
<th>Characteristic</th>
<th>Collagen orientation (cell EM in layer)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial (Gilding zone)</td>
<td>40</td>
<td>↓ Metabolic activity</td>
<td>Tangential</td>
<td>Opposes shear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Highest [H₂O]</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Highest [Lubricin]</td>
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<tr>
<td></td>
<td></td>
<td>Flat chondrocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle zones (Transitional and radial)</td>
<td>500 – 1000</td>
<td>↑ Metabolic activity</td>
<td>Oblique to vertical</td>
<td>Opposes compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Cell size</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Collagen size</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ [Proteoglycan]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Lowest [H₂O]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcified zone (Begins at tidemark)</td>
<td>300</td>
<td>Ca²⁺ crystals</td>
<td>As an anchor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Hydroxypatite)</td>
<td></td>
<td>opposes shear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type X collagen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Continuous passive motion is believed to benefit cartilage healing
• Four weeks of immobilization decreases proteoglycans/collagen ratio
• Ratio returns to normal after 8 weeks of joint mobilization
• Joint instability allows abnormal shearing loads
  • Early (≤4 weeks): proteoglycan/collagen ratio is decreased.
  • Late (≥12 weeks): proteoglycan/collagen is elevated and hydration is increased.
  • Instability markedly reduces hyaluronan (disuse does not).
• Beneficial effects of exercise
  • Increased glycosaminoglycans
  • Runners may have increased cartilage thickness
  • Likely due to chondrocyte modulation through mechanotransduction
• Growth factors and cartilage injury
  • IL-1 stimulates MMP, COX-2, and nitric oxide synthetase, which degrades cartilage.
  • TGF-β stimulates synthesis of ECM and decreases activity of IL-1 and MMPs
    • Also stimulates chondrogenesis in vitro
  • BMP-2, BMP-7, and IGF-1 also stimulate ECM production
• Changes with aging (see Fig. 1.26)
  • Decreased number of chondrocytes (but larger in size)
  • Increased lysosomal enzymes
  • Senescence markers of chondrocytes include telomere erosion, higher β-galactosidase expression, and reduced Wnt2 expression
  • Lower response to growth factors (TGF-β)
    • Decreased matrix production and matrix maintenance
    • Decreased chondroitin SO₄⁻ (but increased keratan SO₄⁻)
• Proteoglycan molecules smaller, so less able to hold water (lower water content)
• Increase in advanced glycosylation end products
  • Yellows and stiffens cartilage
  • Greater stiffness or modulus of elasticity but less tensile strength
    • Increased decorin—decorates collagen for cross-links
    • Increased collagen cross-links and diameter
  • “Dried up old cartilage is yellow, weak, brittle, & stiff”
• Changes with osteoarthritis
  • Increase in cells early (cloning)
  • Loss of smooth lamina leads to fibration/fissures.
    • Higher coefficient of friction
  • Chondrocytes react to IL-1β and TNF and produce nitric oxide
• IL-1 stimulates MMPs, which degrade matrix.
  • Collagenases (MMP-13)—first irreversible step
  • Aggrecanase—degrade proteoglycans (ADAMTs)
  • Stromelysin
  • Decreased size and content of proteoglycan molecules
  • Decreased keratan SO₄⁻ and increased chondroitin/keratan ratio
  • Increase in percentage of nonaggregated glycosaminoglycans
  • Higher water content and greater permeability initially followed by lower water content in later stages
• Decreased modulus of elasticity (less stiff) and tensile strength
• Other periarticular tissue
• Synovium
  • Loose connective tissue rich in capillaries
  • Lacks a basement membrane; no tight junctions
  • Type A synovial cells—macrophage-like
    • Involved in phagocytosis
  • Type B synovial cells derived from mesenchymal cells—fibroblast-like
    • Produce synovial fluid and lubricin
• Lubricin
  • Mucinous glycoprotein that binds to hyaluronic acid
  • Also present in lamina splendens
  • Contributes to boundary lubrication
    • Lubricant is present between two surfaces but its thickness is inadequate to prevent contact throughout the surfaces
  • Defect associated with camptodactyly-arthritis—coxal vara—pericarditis (CACP) syndrome
  • Elastohydrodynamic lubrication
    • Major mode of lubrication in joints
  • Lubricant pressure causes elastic deformation of the opposing surfaces.
    • This elastic deformation increases conformity.
• Synovial fluid
  • Ultrafiltrate of plasma
  • Hyaluronic acid, lubricin, proteinase, collagenases, and prostaglandins
  • Nourishes and lubricates cartilage
  • Contributes to boundary lubrication
  • Normally contains no RBCs, WBCs, or clotting factors
• Joint fluid analysis
  • Noninflammatory arthritis
    • Clear, straw color, high viscosity
    • WBCs: fewer than 200 cells/μL, with 25% polymorphonuclear leukocytes (PMNs)
  • Inflammatory arthritis
    • Yellow-green tinged with low viscosity
    • WBC count: 200–75,000 cells/μL, up to 50% PMNs
    • Complement is decreased in rheumatoid arthritis (RA) (normal in ankylosing spondylitis [AS])
    • Crystals seen in gout and calcium pyrophosphate (dihydrate crystal) deposition disease (CPDD)
  • Septic arthritis
    • Cloudy to opaque
    • WBC count above 50,000–80,000 cells/μL
    • Low glucose and high lactate may also be seen
  • Traumatic
    • Increased RBC and protein values
    • Concern for intraarticular fracture if fat globules present
    • MRI neapolitan effusion—fat above plasma above RBCs
• Meniscus (labrum in hip/shoulder)
  • Increases contact area and distributes load
  • Deepens the articular surfaces of various synovial joints
  • 90% type I collagen
  • Fibroelastic cartilage
  • Fibrochondrocyte is responsible for meniscal healing
  • More elastic and less permeable than articular cartilage
- Blood supplies only the peripheral 25% of the knee menisci.
- Nerve fibers found in peripheral two-thirds.

**Arthritides (Table 1.20)**

- **Osteoarthritis**
  - Progressive loss of cartilage structure and function
  - Most common form of arthritis
  - May be idiopathic
  - May be secondary to:
    - Genetics (Col2 defect); women affected more than men
    - Overload: obesity, labor, dysplasia/ilemal acetabular impingement, varus/valgus
    - Trauma: fractures, ligament injuries, impact
  - Tissue changes:
    - Cartilage: enzymatic degradation and loss as discussed previously (Fig. 1.30)
    - Synovium: inflammation, vascular hypertrophy
    - Ligaments: tightened on concave side of deformity
    - Bone: sclerosis, osteophytes, and subchondral cysts
  - **Osteophyte formation due to pathologic activation of endochondral ossification by periaricular chondrocytes through Indian hedgehog (Ihh) mechanism**
    - Muscles: atrophied from inactivity
  - Radiographic findings (Figs. 1.31 and 1.32)
    - Joint space narrowing, often asymmetric, with osteophyte formation
    - Effusion may show hemarthrosis
    - Histologic findings: osteochondral fragments imbedded in synovium
  - Less pain than would be expected radiographically
  - Etiology: two theories
    - Neuropathic loss of proprioception
    - Repetitive trauma causes microfractures
  - Radiographic findings (Fig. 1.33)
    - Severe destructive changes on both sides of the joint
    - Scattered “chunks” of bone embedded in fibrous tissue
    - Joint distension by fluid
    - Heterotopic ossification
  - Charcot arthropathy versus osteomyelitis
    - May be difficult with physical examination and radiograph
    - Both display swelling, warmth, and erythema and are common in diabetic patients
    - Indium (In) 111-labeled WBC scan results
      - “Hot” (positive) for osteomyelitis
      - “Cold” (negative) for Charcot arthropathy
    - Treatment includes bracing or casting (see Chapter 6)
  - Neuropathic arthropathy also seen in
    - Syringomyelia (see Fig. 1.33C and D)
      - Most common cause of upper extremity neuroarthropathy
      - 80% of cases in shoulder and elbow (see Fig. 1.33D)
      - Joint disease develops in 25% of patients with syringomyelia.
    - Leprosy (Hansen disease)
      - Second most common cause in upper extremity
      - Other neurologic problems
      - Myelomeningocele: ankle and foot
      - Spina bifida and spinal trauma (see Fig. 1.33G)
      - Congenital insensitivity to pain
  - **Rheumatoid arthritis (see Table 1.20)**
    - Most common inflammatory arthritis
    - Affects 0.5%–1% of population; three times more common in women
    - 15% concordance rate in monozygotic twins
    - Clinical presentation (see Fig. 1.32)
      - Insidious subacute onset over 6 weeks
      - Fatigue, malaise, anemia
      - Morning stiffness and polyarthritis with swelling
    - Hand and foot deformities are most common and are discussed in respective subsequent chapters
    - Also common in the knees, elbows, shoulders, ankles, and cervical spine
    - Subcutaneous rheumatoid nodules (Fig. 1.34)
    - Juxtaarticular erosions and periarticular osteopenia on radiographs
    - 2010 American College of Rheumatology Classification Criteria for RA are summarized in Table 1.21.
  - Diagnosis requires score 6 or more
  - Criteria include
    - Number of joints involved and duration of involvement
    - Positive laboratory test results often found
    - Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
    - Rheumatoid factor (RF) titer
      - Antibody (immunoglobulin [Ig] M) against the Fc (crystallizable fragment) portion of IgG
      - Positive result in about 80%
    - Test for anticyclic citrullinated protein (anti-CCP) antibodies
    - Also known as anti-CCP antibodies (ACPAs)
    - Most sensitive and specific test (=90% specific)
    - Presence linked to more aggressive disease
  - **Pathogenesis**
    - T cell–mediated immune response from an infectious or environmental antigen (smoking is one known trigger) in a genetically susceptible individual (HLA-DR4 and HLA-DW4)
    - Mononuclear cells are primary mediator of RA tissue damage
      - Initial response in soft tissues—neovascularization and synovitis
    - CD4+ T lymphocytes (helper cells) activate synovial cells through direct cell-cell contact
    - Synoviocytes produce cytokines
      - Macrophages (type A): main source for TNF-α, IL-1
      - Fibroblast (type B): main source for MMPs, proteases, and RANKL
    - B lymphocytes (plasma cells): make RF, anti-CCP antibodies
      - TNF-α, IL-1, IL-6, IL-7 upregulated
      - IL-1: Regulator of inflammation and matrix destruction
      - TNF-α:
        - Upregulates endothelial adhesion molecules and stimulates angiogenesis
<table>
<thead>
<tr>
<th>ARTHRITIS</th>
<th>AGE GROUP AFFECTED</th>
<th>INCIDENCE BY SEX</th>
<th>SYMMETRY</th>
<th>JOINTS</th>
<th>PHYSICAL EXAMINATION</th>
<th>LABORATORY TESTS</th>
<th>RADIOGRAPHIC FINDINGS</th>
<th>SYSTEMIC MANIFESTATIONS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NONINFLAMMATORY</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Osteoarthritis</td>
<td>Elderly</td>
<td>M &gt; F</td>
<td>Asymmetric</td>
<td>Hip, knee, CMC</td>
<td>I ROM, crepitus</td>
<td>Nonspecific</td>
<td>Asymmetric narrowing, eburnation, cysts, osteophytes</td>
<td>None</td>
<td>NSAIDs, arthrodesis, osteotomy, TJA</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Elderly</td>
<td>M &gt; F</td>
<td>Asymmetric</td>
<td>Foot, ankle, lower extremity</td>
<td>Effusion, unstable</td>
<td>For underlying disease</td>
<td>Destruction/heterotopic bone</td>
<td>None</td>
<td>Brace; TJA contraindicated</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Children</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>Migratory; large joints</td>
<td>Red, tender joint; rash</td>
<td>ASO titer</td>
<td>Usually normal</td>
<td>Erythema marg inatum nodules, carditis</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Ochronosis</td>
<td>Adults</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>Large joints/ spine</td>
<td>I ROM, locking</td>
<td>Urine homogeneous acid</td>
<td>Destruction, disc calcification</td>
<td>Spondylosis</td>
<td>Supportive</td>
</tr>
<tr>
<td><strong>INFLAMMATORY</strong></td>
<td></td>
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<tr>
<td>Rheumatoid</td>
<td>Young adults</td>
<td>F &gt; M</td>
<td>Symmetric</td>
<td>Hands, feet</td>
<td>Ulnar deviation, claw toes</td>
<td>ESR, CRP, RF</td>
<td>Symmetric narrowing, periarticular resorption</td>
<td>Pericardial and pulmonary disease</td>
<td>Pyramid treatment for synovitis, reconstructive surgery</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>Young adults</td>
<td>F &gt; M</td>
<td>Symmetric</td>
<td>PIP joint, MCP joint, knee</td>
<td>Red, swollen joint; rash</td>
<td>ANA</td>
<td>Less destruction</td>
<td>Cardiac, renal, pancytopenia</td>
<td>Drug therapy as for rheumatoid arthritis</td>
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<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>Children</td>
<td>F &gt; M</td>
<td>Symmetric</td>
<td>Knee, multiple</td>
<td>Swollen joint, normal color</td>
<td>RF/ANA</td>
<td>Juxtaarticular late, osteopenia</td>
<td>Iridocyclitis, rash</td>
<td>ASA; 75% remission</td>
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<td>Relapsing polychondritis</td>
<td>Elderly</td>
<td>M = F</td>
<td>Symmetric</td>
<td>All joints</td>
<td>Eye, ear involved</td>
<td>ESR</td>
<td>Normal</td>
<td>Otic, cardiac</td>
<td>Supportive, dapsone?</td>
</tr>
<tr>
<td><strong>SPONDDYLOARTHRopathies</strong></td>
<td></td>
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<tr>
<td>Ankylosing spondylitis</td>
<td>Young adults</td>
<td>M &gt; F</td>
<td>Symmetric</td>
<td>Sacroiliac, spine, hip</td>
<td>Rigid spine, chin on chest</td>
<td>ESR, alkaline phosphatase, CPK, HLA-B27</td>
<td>Sacroiliac arthritis, bamboo spine</td>
<td>Uveitis</td>
<td>Physical therapy, NSAID, osteotomy</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>Young adults</td>
<td>M &gt; F</td>
<td>Asymmetric</td>
<td>Weight-bearing</td>
<td>Urethral discharge, conjunctivitis</td>
<td>ESR, WBC count, HLA-B27</td>
<td>MT head erosion, periostitis</td>
<td>Urethritis, conjunctivitis, ulcer</td>
<td>Physical therapy, NSAID, sulfa?</td>
</tr>
<tr>
<td>Psoriatic</td>
<td>Young adults</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>DIP joint, small joints</td>
<td>Rash, sausage digit, pitting Synovitis, gastrointestinal manifestations</td>
<td>ESR, HLA-B27</td>
<td>DIP joint: pencil-in-cup deformity</td>
<td>Normal</td>
<td>Drug therapy as for rheumatoid arthritis</td>
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<tr>
<td>Enteropathic</td>
<td>Young adults</td>
<td>M &gt; F</td>
<td>Asymmetric</td>
<td>Weight-bearing</td>
<td>Synovitis, gastrointestinal manifestations</td>
<td>ESR, HLA-B27</td>
<td>Erythema nodosum, pyoderma</td>
<td>Drug therapy as for bowel disease, symptomatic therapy</td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>ARTHRITIS</th>
<th>AGE GROUP</th>
<th>INCIDENCE BY SEX</th>
<th>SYMMETRY</th>
<th>JOINTS</th>
<th>PHYSICAL EXAMINATION</th>
<th>LABORATORY TESTS</th>
<th>RADIOGRAPHIC FINDINGS</th>
<th>SYSTEMIC MANIFESTATIONS</th>
<th>TREATMENT</th>
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<tr>
<td><strong>CRYSTAL DEPOSITION DISEASE</strong></td>
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<tr>
<td>Gout</td>
<td>Young</td>
<td>M &gt; F</td>
<td>Asymmetric</td>
<td>Great toe, lower extremity</td>
<td>Tophi, red, swollen</td>
<td>Uric acid: Birefringent crystals</td>
<td>Soft tissue swelling, erosions</td>
<td>Tophi, renal stones</td>
<td>Colchicine, indomethacin</td>
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<tr>
<td>Chondrocalcinosis</td>
<td>Elderly</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>Knee, lower extremity</td>
<td>Acute swelling</td>
<td>Birefringent rhombus-shaped crystals</td>
<td>Articular fibrocartilage calcified</td>
<td>Ochronosis, hyperparathyroidism</td>
<td>Symptomatic therapy; avoid surgery</td>
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<td><strong>INFECTIOUS</strong></td>
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<tr>
<td>Pyogenic</td>
<td>All</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>Any joint</td>
<td>Red, hot, swollen</td>
<td>WBC count, ESR, bacterial cultures</td>
<td>Joint narrowing (late)</td>
<td>Fever, chills, infection</td>
<td>I&amp;D, intravenous antibiotics</td>
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<td>Tuberculous</td>
<td>Elderly</td>
<td>M &gt; F</td>
<td>Asymmetric</td>
<td>Spine, lower extremity</td>
<td>Indolent, swelling</td>
<td>PPD, AFB, cultures</td>
<td>Both sides, cysts</td>
<td>Lung, multiorgan</td>
<td>Antibiotics ± I&amp;D</td>
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<td>Lyme disease</td>
<td>Young</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>Any joint</td>
<td>Acute effusion</td>
<td>Culture, ELISA</td>
<td>Usually normal</td>
<td>Erythema migrans rash, neurologic, cardiac</td>
<td>Penicillin, tetracycline</td>
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<td><strong>HEMORRHAGIC</strong></td>
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<td>Hemophilia</td>
<td>Young</td>
<td>M</td>
<td>Asymmetric</td>
<td>Knee, upper extremity (elbow, shoulder)</td>
<td>↓ ROM, swelling</td>
<td>PTT, factor VIII</td>
<td>Squared-off patella</td>
<td>Soft tissue bleeding</td>
<td>Support, synovectomy, TJA</td>
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<tr>
<td>Sickle cell disease</td>
<td>Young</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>Hip, any bone</td>
<td>Pain, ↓ ROM</td>
<td>Sickle preparation Aspirate, biopsy</td>
<td>Osteonecrosis</td>
<td>Infarcts, osteonecrosis</td>
<td>Supportive and symptomatic therapy</td>
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<tr>
<td>Pigmented villonodular synovitis</td>
<td>Young</td>
<td>M = F</td>
<td>Asymmetric</td>
<td>Knee, lower extremity</td>
<td>Pain, synovitis</td>
<td>None</td>
<td>Juxtacortical erosion</td>
<td>None</td>
<td>Surgical excision</td>
</tr>
</tbody>
</table>

I, Decreased; AFB, acid-fast bacilli; ASO, antistreptolysin O; CPK, creatine phosphokinase; PTT, partial thromboplastin time.
FIG. 1.30 Enzyme cascade of IL-1–stimulated degradation of articular cartilage. TPA, Tissue plasminogen activator. (From Simon SR, editor: Orthopaedic basic science, Rosemont, IL, 1994, American Academy of Orthopaedic Surgeons, p 40.)

FIG. 1.31 (A) Radiograph showing joint space narrowing, osteophytes, and bony sclerosis. (B) Macrosection of an osteoarthritic human femoral head demonstrating subarticular cysts, sclerotic bone formation, and a superior femoral head osteophyte. (C) Low-power micrograph of osteoarthritis showing fibrillation, fissures, and cartilage loss. (D) Gross pathology of femoral head demonstrating cartilage thinning (1), subarticular cyst (2 "geode"), and normal hyaline cartilage remaining (3). (A Courtesy Marc DeHart, MD, and Texas Orthopedics; B from Simon SR, editor: Orthopaedic basic science, Rosemont, IL, 1994, American Academy of Orthopaedic Surgeons; C and D from Horvai A: Bones, joints, and soft tissue tumors. In Kumar V et al, editors: Robbins and Cotran pathologic basis of disease, ed 9, Philadelphia, 2015, Elsevier, Fig. 26-93.)
• Promotes influx of leukocytes and activates synovial fibroblasts
• Promotes pain receptor pathways
• Drives osteoclastogenesis
• Later response
  • Synovial cells invade cartilage “pannus” and release MMPs, causing chondrolysis

• Periarticular bone erosions
• Cytokines stimulate osteoblasts and synovial B cells to make RANKL, which joins with RANK to activate osteoclasts. Responsible for bone destruction.
• Osteoclasts secrete cathepsin K and carbonic anhydrase.

FIG. 1.32 Differences between rheumatoid arthritis and osteoarthritis. Left side of illustration demonstrates the main historical characteristics of RA, including symmetric involvement (both right and left joints as well as both medial and lateral compartments of the knees). Bilateral hand involvement is characteristic and usually involves wrist joints and proximal metacarpal joints. Right side of figure demonstrates osteoarthritis, which often is much more severe in one joint or one compartment of the knee. Hand involvement more commonly involves the distal interphalangeal joints (Heberden nodes) and proximal interphalangeal joints (Bouchard nodes) joints as well as the base of the thumb.
Neuropathic arthritis. Arthritic degeneration due to lack of sensation can be caused by many diseases. All share radiographic findings that are more severe than the symptoms (often painless) and the fragments from bony destruction. Often findings take many years to develop. (A and B) Diabetic Charcot arthropathy of the foot is easily recognized by most of the industrialized world. (C and D) The most common cause of upper extremity neuropathic joint is syringomyelia (syrinx = fluid-filled sac in central cord that causes insidious loss of pain and temperature early). (E–G) Tabetic arthropathy (tertiary syphilis) is the most common neuropathic arthritis of the knee and can often involve the hip. (From Yablon CM et al: A review of Charcot neuroarthropathy of the midfoot and hindfoot: what every radiologist needs to know, Curr Probl Diagn Radiol 39:187–199, 2010; Atalar AC et al: Neuropathic arthropathy of the shoulder associated with syringomyelia: a report of six cases, Acta Orthop Traumatol Turc 44:328–336, 2010; and Allali F et al: Tabetic arthropathy. A report of 43 cases, Clin Rheumatol 25:859–860, 2006.)
- Systemic manifestations
  - Rheumatoid vasculitis
  - Distal splinter hemorrhage
  - Cutaneous ulcers (pyoderma gangrenosum)
  - Visceral arteritis
  - Pericarditis and pericardial effusion
  - Pulmonary disease including nodules and fibrosis
  - Felty syndrome: severe erosive RA with splenomegaly and leukopenia
- Treatments and their perioperative considerations
  - Regimen variable and often employs multiple agents
  - NSAIDs: help symptoms early—antiinflammatory effects
    - Should be held for 7–10 days preoperatively.
  - Low-dose steroids
    - Decrease prostaglandins and leukotrienes
    - Used initially as “bridge therapy” to disease-modifying antirheumatic drugs (DMARDs)
    - “Stress dose” steroid should be used perioperatively for patients on long-term steroid therapy
- DMARDs
  - Intended to address underlying autoimmune response
  - Conventional DMARDs take 2–6 months to work
  - Methotrexate: folate analogue
    - Inhibits purine metabolism and T-cell activation
    - Inhibits neovascularization
    - Adverse reactions (ADRs): toxic to bone marrow, liver, and lung
    - Usually can continue through surgery
  - Azathioprine: immunosuppressive agent
    - ADR: neutropenia
  - Cyclosporine: immunosuppressive agent
    - Inhibits activation of CD4+ T cells
    - ADRs: nephrotoxicity, neurotoxicity, gingival hyperplasia
  - Hydroxychloroquine (Plaquenil)
    - Inhibits toll-like receptor 9 (TLR9)
    - ADR: retinal toxicity (requires ophthalmology follow-up)

**FIG. 1.34** Upper extremity changes in common arthritis types. Left side of figure shows rheumatoid changes. (A) Swan neck deformity of index, middle, and ring fingers, with PIP joints extended and DIP joints flexed. (B) Boutonnière deformity: PIP joints flexed, DIP joints extended. (C) Bilateral wrist swelling with both ulnar metacarpal phalangeal joint deformities and swan neck deformities of fingers and left thumb. (D) Rheumatoid nodes noted on posterior olecranon region. Right side of figure shows osteoarthritic changes. (E) DIP changes (Heberden nodes) and PIP changes (Bouchard nodes). (F) Radiograph showing osteoarthritic changes at the base of the thumb. (From O’Dell JD: Rheumatoid arthritis. In Goldman L, Schafer Al, editors: Goldman-Cecil medicine, Philadelphia, 2016, Elsevier, Fig. 264-3; Sweeney SE et al: Clinical features of rheumatoid arthritis. In Firestein GS et al: Kelley’s textbook of rheumatology, Philadelphia, 2013, Elsevier, Fig. 70-4; and http://medsci.indiana.edu/c602web/602/c602web/jtcs/docs/heber1.html.)
Table 1.21  

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. JOINT INVOLVEMENT</strong></td>
<td></td>
</tr>
<tr>
<td>1 Large Joint</td>
<td>0</td>
</tr>
<tr>
<td>2–10 Large Joints</td>
<td>1</td>
</tr>
<tr>
<td>1–3 Small Joints</td>
<td>2</td>
</tr>
<tr>
<td>4–10 Small Joints</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 Joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>B. SEROLOGY (at least 1 test result is needed)</strong></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive ACPA</td>
<td>3</td>
</tr>
<tr>
<td><strong>C. ACUTE-PHASE REACTANTS (at least 1 test result is needed)</strong></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>D. DURATION OF SYMPTOMS</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>&gt;6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>


- Usually can continue through surgery
- Sulfasalazine
- Decreases synthesis of inflammatory mediators
- ADRs: granulocytopenia, hemolytic anemia (glucose-6-phosphate dehydrogenase [G6PD])
- Usually can continue through surgery
- Minocycline
- Inhibits MMP collagenase
- ADR: cutaneous hyperpigmentation
- Biologic DMARDs
- Target TNF-α: etanercept, infliximab, adalimumab
- Targets IL-1: anakinra
- Targets CD20: rituximab
- Surgery should be scheduled at end of dosing cycle (e.g., in a patient taking etanercept schedule, surgery should occur the second week after the first withheld dose).
- **Risks of opportunistic infection and lymphoma**
  - Surgical treatment is discussed within respective chapters.

- Juvenile idiopathic arthritis (JIA) is discussed in Chapter 3, Pediatric Orthopaedics.
- Systemic lupus erythematosus (Fig. 1.35; see Table 1.20)
  - Chronic inflammatory disease of unknown origin
  - 90% of cases in women (blacks > whites)
  - Initially mediated by tissue-binding autoantibodies and immune complexes (type III hypersensitivity)
  - Pathophysiology
    - Susceptible genetics stimulated by environment
    - Immune system autoregulatory failure
    - Sustained production of antibody to self-antigens
    - Antinuclear antibodies (ANAs)—best screen; positive in 95%
    - Anti-dsDNA, anti-Sm, anti-La (SS-B), antihistone antibodies—drug-induced lupus
    - Immune complexes accumulate in various tissues and cause chronic inflammation
    - Skin/joints—rash and arthritis
    - Heart/kidney—pericarditis/nephritis
    - Blood vessels—vasculitis
    - Clinical findings
      - Bone and joint involvement—most common feature
      - Nonsesive polyarthritis affects over 75% (hand and wrist most common).
      - Osteonecrosis (especially with steroids)
      - Butterfly malar rash—classic feature
      - Fever, pancytopenia
      - Pharmacologic treatment similar to that for RA.
- Seronegative spondyloarthropathies
  - Characterized by negative RF titer result and, often, positive HLA-B27 test result
  - Symptoms
    - Inflammatory back pain
    - Peripheral arthritis
    - Enthesitis—heel pain
    - Dactylitis—sausage digit
    - Eye—uveitis (iritis), conjunctivitis
    - Skin, mucosal, GI, urethral
    - Similar treatment routines, including NSAIDs, steroids, and DMARDs
- Ankylosing spondylitis (AS) (Fig. 1.36; see Table 1.20)
  - Male/female ratio 3:1; ages 20–40 years
  - Most common in Northern European whites
  - 90% HLA-B27 positive (Table 1.22)
  - Symptoms and findings
    - Bilateral sacroiliitis (earliest symptom)
    - Improves with exercise, not better with rest, pain at night
    - Associated morning stiffness
    - Progressive spinal flexion deformities over life
    - Chin-on-chest deformity
    - Modified Schober test (loss of lumbar flexion) (see Fig. 1.36C)
      - Two marks are made10 cm apart over lumbar spine in erect patient.
      - With patient in maximum spinal flexion, increase of less than 4 cm between marks indicates loss of flexion.
    - Hip involvement at young age—poor prognosis
    - Enthesitis: inflammation of tendon insertion
    - Loss of chest expansion
    - Uveitis: red, painful eye in 40%
    - Aortic insufficiency and heart block
    - Radiographic changes
      - Squaring of the vertebrae
      - Vertical syndesmophytes
      - Bamboo spine
      - Autofusion of sacroiliac joints (see Fig. 1.36B)
      - Whiskering of the entheses
    - Surgical treatment for AS is discussed within Chapter 8, Spine.
- Reactive arthritis (Reiter syndrome) (Fig. 1.37; see Table 1.20)
  - Classical triad presentation: “Can’t see, can’t pee, can’t climb a tree.”
  - Young white males (18–40 years)
  - Follows an infection at another site (hence “reactive”)
    - *Chlamydia, Shigella, Yersinia, Salmonella*
    - Findings
      - Conjunctivitis, urethritis, and oligoarticular arthritis
• Sudden asymmetric swelling and pain in knee, ankle, hip
• May persist 3–5 months
• Feet affected more often than hands (heel pain)
• Calcaneal periostitis and metatarsal head erosion
• Dactylitis: sausage digit of one fingertoe (see Fig. 1.37E)
• 60% of patients with chronic disease have sacroiliitis.

• Painless mucocutaneous ulcers (penile) and oral stomatitis (see Fig. 1.37B)
• Urethritis (dysuria), prostatitis, or cervicitis
• Pustular lesions on the extremities, palms, and soles (keratoderma blennorrhagicum)
• Treatment: NSAIDs and PT
Psoriatic arthropathy (PsA) (see Table 1.20)
- Affects 5%–30% of patients with psoriasis
- Usually skin disease precedes arthritis
- Men and women (aged 30–40 years) equally affected
- Characteristic changes
  - Distal interphalangeal (DIP) involvement (rare in other inflammatory arthritides)
  - Nail changes in 90%
    - Pitting, fragmentation, and discoloration
  - 30% have sausage digits
  - Prominent enthesitis and tenosynovitis
  - Arthritis mutilans—most destructive form
  - Telescoping (shortening) of digits
- Pathophysiology
  - Upregulated RANKL in synovium (B-type cells)
  - Marked increase in osteoclast precursors
- Radiographic findings
  - Pencil-in-cup deformity, DIP
  - Small joint ankylosis
  - Osteolysis of metacarpal (MC) and phalangeal bone
  - Periostitis and bony enthesitis

Enteropathic arthritis (see Tables 1.20 and 1.22)
- Arthritis in presence of inflammatory bowel disease
- Varied clinical picture, but joint erosions uncommon
- 10%–50% of patients experience peripheral joint arthritis.
  - Acute monoarticular synovitis precedes bowel symptoms.
  - Nondeforming arthritis
  - More common in large weight-bearing joints
  - 10%–15% of cases associated with ankylosing spondylitis

Crystal deposition arthropathy
- Pathology from accumulation of crystal formation or deposition in or around joints
  - Gout: monosodium urate
  - CPDD, also called pseudogout: calcium pyrophosphate
  - Tumoral calcinosis: calcium apatite
  - Calcium oxalate

Gout (see Table 1.20)
- Disorder of purine nucleic acid metabolism, causing hyperuricemia
- Deposition of monosodium urate crystals in joints
- Crystals activate inflammatory mediators
  - Inflammatory mediators are inhibited by colchicine.
- Attacks precipitated by dehydration, excess alcohol or dietary purines, chemotherapy
- Diagnosis
  - Recurrent acute joint pain
  - Men aged 40–60 years, postmenopausal women
  - Usually lower extremity; great toe (podagra)
  - Crystal deposition as tophi when chronic
    - Ear helix, eyelid, olecranon, Achilles tendon
  - Renal disease or stones—second most common site
- Radiographic findings
  - Soft tissue swelling early: edema, tophi
  - Punched-out or rat bite periarticular erosions
  - Sclerotic overhanging borders
- Synovial fluid findings
  - Concomitant septic arthritis must be ruled out
  - WBC count: wide range (5,000–80,000 cells/μL; average, 15,000–20,000 cells/μL), mostly PMNs

**FIG. 1.36** Ankylosing spondylitis is an axial seronegative spondyloarthropathy that causes progressive cervical and thoracic kyphosis and bamboo spine but has earliest involvement in the sacroiliac joints. (A) Early sacroiliitis demonstrated by loss of clarity and sclerosis in the lower third of the sacroiliac joints, particularly affecting the iliac side of the right sacroiliac joint (hip joints are normal). (B) Advanced disease with ankylosis or fusion of both the sacroiliac and hip joints. (C) Schober test; two marks made 10 cm apart on lumbar spine in erect stance should be less than 14 to 15 cm during forward flexion. (From Raychaudhuri S. The classification and diagnostic criteria of ankylosing spondylitis, *J Autoimmun* 48–49:128–133, 2014.)
### Table 1.22 Associations Between HLA Alleles and Susceptibility to Some Rheumatic Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>HLA MARKER</th>
<th>FREQUENCY (%) IN PATIENTS (WHITES)</th>
<th>FREQUENCY (%) IN CONTROLS (WHITES)</th>
<th>RELATIVE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>90</td>
<td>9</td>
<td>87</td>
</tr>
<tr>
<td>Reactive arthritis (Reiter syndrome)</td>
<td>B27</td>
<td>79</td>
<td>9</td>
<td>37</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>B27</td>
<td>48</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Inflammatory bowel disease with spondylitis</td>
<td>B27</td>
<td>52</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Adult rheumatoid arthritis</td>
<td>DR4</td>
<td>70</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Polyarticular juvenile rheumatoid arthritis</td>
<td>DR4</td>
<td>75</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Pauciarticular juvenile rheumatoid arthritis</td>
<td>DR8</td>
<td>30</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>DR5</td>
<td>50</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>DR2.1</td>
<td>55</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DR2</td>
<td>46</td>
<td>22</td>
<td>3.5</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>DR3</td>
<td>50</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>DR3</td>
<td>70</td>
<td>25</td>
<td>6</td>
</tr>
</tbody>
</table>

- Yellow, needle-shaped crystals when parallel to compensator (Fig. 1.38A)
- Strong negative birefringence
- Treatment:
  - NSAIDs and colchicine (microtubule inhibitor that inhibits mitosis) for acute attack
  - Chronic/maintenance therapy
  - Weight loss, low-purine diet, limit of alcohol intake
  - Probenecid: uricosuric agent
  - Allopurinol: xanthine oxidase inhibitor
  - Febuxostat in renally impaired patients

Pseudogout (see Table 1.20)
- Deposition of calcium pyrophosphate dehydrate (CPPD) crystals in joints
- Associated with lupus, renal dialysis, hemochromatosis, hyperparathyroidism, RA, Wilson disease
- Chondrocalcinosis
- Calcification within hyaline or fibrocartilage or menisci
- Seen in pseudogout but also in other conditions
- Genetic version: ANKH gene mutation
- Increases extracellular pyrophosphate
- Synovial fluid findings
  - WBC counts 5000–100,000 cells/μL (average, 24,000 cells/μL)
  - Rhomboid-shaped crystals in WBCs
  - Weakly positively (blue) birefringent when parallel (see Fig. 1.38B)
- Radiographic findings: fine linear calcification in hyaline cartilage and more diffuse calcification of menisci and other fibrocartilage (triangular fibrocartilage complex, acetabular labrum)
- Treatment with NSAIDs and, potentially, steroid injection

Calcium hydroxyapatite crystal deposition disease
- Apatite is primary crystal of normal bone.
- Accumulates abnormally in areas of tissue damage or in hypercalcemic or hyperparathyroid states (chronic kidney disease [CKD])
- Associated with
  - Acute attacks of bursitis/synovitis

Severe degenerative joint disease
- Calcific tendinitis of rotator cuff and hip abductors
- Destructive arthropathy can occur in the knee and shoulder.
- Milwaukee shoulder: calcium phosphate deposition with cuff tear arthropathy

Calcium oxalate deposition
- Primary oxalosis—rare genetic defect of liver enzymes
  - Alanine glyoxylate aminotransferase (AGT)
  - Glyoxylate reductase (GR)
- Nephrocalcinosis, renal failure, and death by age 20 years
- Treatment: liver/kidney transplantation
- Secondary oxalosis—more common
  - Metabolic abnormalities of chronic renal insufficiency
  - Associated with calcium oxalate arthritis/periartthritis and nephrolithiasis
  - Diagnosis: synovial fluid usually contains fewer than 2000 WBCs/μL.
  - Birefringent bipyramidal crystals (see Fig. 1.38C)

Hemophilic arthropathy (Fig. 1.39)
- X-linked recessive defect of factor VIII (A) or IX (B); discussed further in Chapter 3, Pediatric Orthopaedics
- Decreased ROM and eventually ankylosis

Pathophysiology
- Recurrent bleeds and chronic synovitis
- Synovial hypertrophy/hyperplasia
- Iron-laden phagocytic type A synovial cells
- Synovium destroys cartilage

Radiographic findings
- Flat condylar surface and widened notch in knee
- Inferior patellar squaring
- Talar flattening in ankle

Treatment
- Early: prevention of bleeds/factor replacement
- Radiation ablation of synovium with yttrium (Y) 90 microspheres and phosphorus (P) 32 colloid
- Late: arthroplasty

**FIG. 1.38** Synovial fluid crystals. (A) Gout: yellow uric acid parallel to compensator, most common in first metatarsophalangeal joint. (B) Calcium pyrophosphate (dihydrate crystal) deposition disease (CPDD) or pseudogout crystals: blue rhomboid crystals (arrow) most common in knees and wrists. (C) Calcium oxalate crystals (arrow) are pyramidal and almost exclusively seen in patients with renal damage and oxalosis. (D) Plate-like cholesterol crystals are rare and can be found in inflammatory synovial fluid and in fluids drained from bursas of patients with rheumatoid arthritis, systemic lupus erythematosus, and seronegative spondyloarthropathy. (E) Calcium apatite crystals from tumoral calcinosis on histology slide from tissue. (From McPherson RA, Pincus MR, editors: Henry’s clinical diagnosis and management by laboratory methods; ed 21, Philadelphia, 2007, Saunders Elsevier; Firestein GS et al, editors: Kelley’s textbook of rheumatology, ed 8, Philadelphia, 2008, Saunders; Courtney P, Doherty M: Joint aspiration and injection and synovial fluid analysis, Best Pract Res Clin Rheumatol 23:161–192, 2013; Martinez-Castillo A et al: Synovial fluid analysis, Rheumatol Clin 6:316–321, 2010; and Topaz O et al: A deleterious mutation in SAMD9 causes normophosphatemic familial tumoral calcinosis, Am J Hum Genet 79:759–764, 2006.)
Basic Sciences

MUSCLE

- **Skeletal muscle anatomy (Fig. 1.40)**
  - **Cellular anatomy**
    - Sarcolemma: plasma membrane surrounding cell

- **Sarcolemma**
  - Extends into cell surrounding myofibrils
  - Forms the transverse tubules (Fig. 1.41).
  - Multiple nuclei: typically located adjacent to sarcolemma

- **Sarcomplasmic reticulum (SR)**
  - Smooth endoplasmic reticulum that surrounds the individual myofibrils
  - Stores calcium in intracellular membrane-bound channels.
  - Ryanodine receptors (e.g., RYR-1) regulate the release of calcium from the SR and serve as a connection between the SR and sarcolemma-derived transverse tubule.
  - Abnormality of ryanodine receptors is implicated in persons susceptible to malignant hyperthermia.
  - Dantrolene decreases loss of calcium from the SR.

- **Contractile elements**
  - **Sarcomere**: basic functional unit of muscle contraction
  - **Myofibrils**
    - Set of sarcomeres parallel to axis of cell
    - (1–3 μm in diameter and 1 μm ² cm long)
  - **Sarcomere organization causes the banding pattern (stripes) seen in skeletal muscle (Table 1.23; see Fig. 1.40).**
    - Costamere connects the sarcomere to the sarcolemma at the Z disc.
    - Z disc (or line) represents terminus of sarcomere
    - Contains desmin, α-actinin, and filamin
    - A-band (or dark band) represents thick filaments.
      - Thick filaments composed of myosin
        - Also contains myosin [H-band], M protein, C protein, titin, and creatine kinase
    - I-band represents thin filaments.
      - Primarily composed of actin
      - Also contains
        - Troponin: has binding site for Ca
        - Tropomyosin: prevents myosin-actin interaction
  - **Attach to Z disc**
  - Involved in delayed-onset muscle soreness (DOMS)

- **Gross anatomy**
  - Fascia (tough connective tissue) covers muscle and allows sliding.
  - Epimysium (more delicate) surrounds bundles of fascicles.
  - Perimysium surrounds individual muscle fascicles (hundred of muscle fibers).
  - Endomysium surrounds individual myofibers.
  - **Stretch receptors**
    - Muscle spindles: located within muscle, transmit muscle length to CNS, control muscle stiffness
    - Golgi tendon organ: located at musculotendinous junction, helps prevent excess tendon lengthening
  - **Myotendinous junction**
    - Often the site of tears with eccentric contraction (forced lengthening of the myotendinous junction during contraction), which places maximum stress across this area
  - **Myofilament bundles are linked directly onto collagen fibrils, with sarcolemma filaments interdigitating with the basement membrane (type IV collagen) and tendon tissue (type I collagen).**

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FIG. 1.41 Sarcoplasmic reticulum. Action potentials travel down the transverse tubules, causing release of calcium from the outer vesicles. (From DeLee JC et al, editors: DeLee and Drez's orthopaedic sports medicine: principles and practice, ed 3, Philadelphia, 2009, Saunders.)

<table>
<thead>
<tr>
<th>Band</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A band</td>
<td>Contains actin and myosin</td>
</tr>
<tr>
<td>I band</td>
<td>Contains actin only</td>
</tr>
<tr>
<td>H band</td>
<td>Contains myosin only</td>
</tr>
<tr>
<td>M line</td>
<td>Interconnecting site of the thick filaments</td>
</tr>
<tr>
<td>Z line</td>
<td>Anchors the thin filaments</td>
</tr>
</tbody>
</table>

Muscle physiology

Motor unit
- The α-motoneuron and the myofibers it innervates
- Each myofiber is innervated by a single axon but an axon can innervate multiple myofibers
- Smaller and more delicate muscles have fewer myofibers per motor unit (<5 fibers per unit in extraocular muscles but as many as 1800 fibers per unit in gastrocnemius muscle)

Contraction
- Response to mechanical or electrochemical stimuli generated at the motor end plate (neuromuscular junction) where the axon contacts an individual myofiber (Fig. 1.42).
- Depolarization reaches motor neuron axon terminal, and acetylcholine (ACh) is released from presynaptic vesicles.

- ACh diffuses across the synaptic cleft (50 nm) and binds to postsynaptic receptors on sarcolemma, which begin depolarization.
- Myasthenia gravis is due to IgG antibodies to the ACh receptor. Manifests initially as ptosis and diplopia. Weakness worse with muscle use.
- Botulinum A injections reduce spasticity by blocking presynaptic acetylcholine release. Commonly used for spastic muscles in cerebral palsy.
- Agents affecting impulse transmission are listed in Table 1.24.
- Sarcoplasmic reticulum releases calcium.
- Ca binds to troponin and causes conformational change, which stops tropomyosin inhibition of myosin-actin cross-bridges.
- Myosin binds to actin, hydrolyzes ATP, and “pushes” actin on thin filament, leading to muscle contraction.
Types of muscle contractions are summarized in Table 1.25:
- Muscle cross-sectional area is a reliable predictor of the potential for contractile force.
- Muscle tension is determined by the contractile force generated.
- Muscle contraction velocity is determined by fiber length.
  - A well-conditioned muscle may be able to fire more than 90% of its fibers simultaneously.
  - At any velocity, fast-twitch (type II) fibers produce more force.
- Isokinetic exercises produce more strength gains than do isometric exercises (see Table 1.25).
- Plyometric (“jumping”) exercises, the most efficient method of improving power, consist of a muscle stretch followed immediately by a rapid contraction.
- Closed-chain exercise involves loading an extremity with the most distal segment stabilized or not moving, allowing for muscular cocontraction around a joint and minimizing joint shear (e.g., less stress on the ACL).
- Open-chain exercise involves loading an extremity with the distal segment of the limb moving freely (e.g., biceps curls).

Types of muscle fibers (Table 1.26)
- Subtypes are based on variability in myosin heavy chains
  - Type I
    - Slow-twitch, oxidative, “red” fibers (mnemonic: “slow red ox”)
    - Aerobic
    - Have more mitochondria, enzymes, and triglycerides (energy source) than type II fibers
    - Low concentrations of glycogen and glycolytic enzymes (ATPase)
    - Enable performing endurance activities, posture, balance
    - Are the first lost without rehabilitation
  - Type II
    - Fast-twitch, glycolytic, “white” fibers
    - Anaerobic
    - Contract more quickly and have larger, stronger motor units (increased ATPase) than type I fibers
    - Less efficient than type I but with large amount of force per cross-sectional area, high contraction speeds, and quick relaxation times
    - Well suited for high-intensity, short-duration activities (e.g., sprinting)

### Table 1.24 Agents That Affect Neuromuscular Impulse Transmission
<table>
<thead>
<tr>
<th>AGENTS</th>
<th>SITE OF ACTION</th>
<th>MECHANISM</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondepolarizing drugs (curare, pancuronium, vecuronium)</td>
<td>Neuromuscular junction</td>
<td>Competitively bind to acetylcholine receptor to block impulse transmission</td>
<td>Paralytic agents (long term)</td>
</tr>
<tr>
<td>Depolarizing drugs (succinylcholine)</td>
<td>Neuromuscular junction</td>
<td>Bind to acetylcholine receptor to cause temporary depolarization of muscle membrane</td>
<td>Paralytic agents (short term)</td>
</tr>
<tr>
<td>Anticholinesterases (neostigmine, edrophonium)</td>
<td>Autonomic ganglia</td>
<td>Prevent breakdown of acetylcholine to enhance its effect</td>
<td>Reverse effects of nondepolarizing drugs; muscarinic effects (bronchospasm, bronchorrhea, bradycardia)</td>
</tr>
</tbody>
</table>

### Table 1.25 Types of Muscle Contractions
<table>
<thead>
<tr>
<th>TYPE OF MUSCLE CONTRACTION</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
<th>PHASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic</td>
<td>Muscle tension is constant throughout ROM. Muscle length changes throughout ROM. This is a measure of dynamic strength.</td>
<td>Biceps curls with free weights</td>
<td>Concentric contraction: Muscle shortens during contraction. Tension within muscle is proportional to externally applied load. Example of an isotonic concentric contraction is the curl (elbow moving toward increasing flexion) portion of a biceps curl. Eccentric contraction: Muscle lengthens during contraction (internal force &lt; external force). Eccentric contractions are the most efficient way to strengthen muscle but have the greatest potential for high muscle tension and muscle injury. Example of an isotonic eccentric contraction is the negative (elbow moving toward increasing extension) portion of a biceps curl.</td>
</tr>
<tr>
<td>Isometric</td>
<td>Muscle tension is generated, but muscle length remains unchanged. This is a measure of static strength.</td>
<td>Pushing against an immovable object (e.g., wall)</td>
<td></td>
</tr>
<tr>
<td>Isokinetic</td>
<td>Muscle tension is generated as muscle maximally contracts at a constant velocity over a full ROM. Isokinetic exercises are best for maximizing strength and are a measure of dynamic strength.</td>
<td>Isokinetic exercises require special equipment (e.g., Cybex machine)</td>
<td>Concentric contraction</td>
</tr>
<tr>
<td>Eccentric contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Rapid fatigue
• Low intramuscular triglyceride stores
• Two subtypes:
  • Type IIA is intermediate.
  • Type IIB is most fatigable and has highest anaerobic capacity.

### Energetics (Fig. 1.43)
- **ATP-creatine phosphate (phosphagen) system**
  - Converts stored carbohydrates to energy without the use of oxygen and without producing lactate.
  - Intense muscle activities lasting up to 20 seconds (sprinting)
  - Creatine supplementation can increase work produced in the first few maximum-effort anaerobic trials but does not increase peak force production.
  - Creatine shifts fluid intracellularly; the shift may present a risk for dehydration, although cramps are the more common side effect.
- **Lactic anaerobic system (lactic acid metabolism)**
  - Muscle glycogen and blood glucose anaerobically converted to ATP
  - Incomplete oxidation leads to excess pyruvate, which is converted to lactic acid (via lactate dehydrogenase)
  - Intense muscle activities lasting 20 to 120 seconds
- **Aerobic system**
  - Aerobic oxidation of glycogen and fatty acids through Krebs cycle
  - Sustained exercise such as distance running

### Athletic training, injury, and adaptation
- **Training**
  - Specific training can selectively alter fiber composition.
  - Endurance athletes—higher percentage of slow-twitch fibers
  - Sprinters and athletes in “strength” sports—higher percentage of fast-twitch fibers
  - Endurance training—decreased tension and increased repetitions
  - Induces hypertrophy of slow-twitch fibers
  - Increases capillary density, mitochondria, and oxidative capacity
  - Increases resistance to fatigue and cardiac output
  - Improves blood lipid profiles
  - Strength training—increased tension and decreased repetitions
  - Induces hypertrophy (increased cross-sectional area) of fast-twitch (type II) fibers
  - Induces myofibrillar muscle protein synthesis (MPS)
  - Improves neural activation
  - Both endurance training and strength training delay the lactate response to exercise.
  - A significant decline in aerobic fitness (“detraining”) occurs after only 2 weeks of no training.
- **Denervation**
  - Causes muscle atrophy and increased sensitivity to acetylcholine
  - Leads to spontaneous fibrillations at 2–4 weeks after injury
- **Immobilization**
  - Accelerates granulation tissue response
  - Immobilization in lengthened positions decreases contractures and maintains strength.
  - Atrophy results from disuse or altered recruitment.
  - Muscles that cross a single joint atrophy faster (nonlinear fashion).
  - Sarcomeres at the myotendinous junction are especially affected
  - Electrical stimulation can help offset these effects.
- **Muscle strains**
  - Most common sports injury
  - Most occur at the myotendinous junction.
  - Occur primarily in muscles crossing two joints (hamstring, gastrocnemius) that have increased type II fibers
  - Initially there is inflammation, and later, fibrosis mediated by TGF-β occurs.
  - **Immobilization or rest for 3–5 days followed by progressive stretching and strengthening**
  - **Muscle tears**
    - Most occur at the myotendinous junction (e.g., rectus femoris tear at anterior inferior iliac spine).
    - Often occur during a rapid (high-velocity) eccentric contraction
Satellite cells act as stem cells and are most responsible for muscle healing.
- Alternatively, the defect can heal with bridging scar tissue. TGF-β stimulates proliferation of myofibroblasts and increases fibrosis.
- Surgical repair of clean lacerations in the muscle midbelly usually results in minimal regeneration of muscle fibers distally, scar formation at the laceration, and recovery of about half the muscle strength.
- Prevention of tears—muscle activation (through stretching) allows twice the energy absorption before failure.

**DOMS**
- This phenomenon occurs 24–72 hours after intense exercise.
- Associated with eccentric muscle contractions
  - Most common in type IIB fibers
  - Caused by edema and inflammation in the connective tissue, with a neutrophilic response present after acute muscle injury
  - May be associated with changes in the I band of the sarcomere
  - NSAIDs relieve DOMS in a dose-dependent manner.
  - Other modalities (ice, stretching, ultrasonography, electrical stimulation) have not been shown to affect DOMS.

**TENDON** *(Fig. 1.44)*

**Structure and composition**

**Composition**
- Water: 50%–60% of total tendon weight
- Collagen: 75% of dry weight
  - 95% type I collagen, also type III collagen
- Elastin: 1%–2% of dry weight
  - Highly elastic protein that allows tendon to resume its shape after stretching

**Structure**
- Strands of collagen (triple helix of two α1 chains and one α2 chain) organized into microfibrils, which in turn make up fibrils, fascicles, and tendon
- Fascicles surrounded by endotendon (contiguous with epitendon covering entire tendon)
- Carry the neurovascular and lymphatic supply of tendons
- Composed of type III collagen
- With aging, more type I collagen strands interdigitate between type III collagen strands.
- Covered by paratenon (Achilles, patellar tendons) versus synovium (digital flexor tendons)
- Higher vascularity of paratenon leads to increased healing.

**Sheathed tendons**
- **Vincula (extension of synovium) carry blood supply to one tendon segment** *(Fig. 1.45)*.
- Some nutrition from synovial fluid (found between the two layers of the synovial sheath) via diffusion
- **Myotendinous junction**
  - Actin microfilaments extend from the last Z line
  - These are linked to the sarcolemma, which in turn connects to the collagen fibril–rich matrix of the tendon.
- **Bone-tendon junction (direct vs. indirect)**
  - Direct (fibrocartilaginous) insertion
    - Usually in areas subject to high tensile load
    - Four layers: tendon, fibrocartilage, mineralized fibrocartilage, and bone
  - Indirect Insertion
    - Fibers insert directly into periosteum through Sharpey fibers

**Mechanical properties**
- Anisotropic: properties vary depending on direction of applied force
- Viscoelastic: properties vary depending on rate of force application
Basic Sciences

Creep: increasing deformation under constant load
Stress relaxation: decreasing stress with constant deformation (elongation)
Hysteresis: during loading and unloading, the unloading curve is different from the loading curve. The difference between the two represents the amount of energy that is lost during loading.

Stress-strain curve
- Rest: collagen fibers are “crimped.”
- Toe region: flattening of crimp; nonlinear; tendon stretched easily
- Linear region: intermediate loads
- Failure

Injury and healing
Three stages of tendon healing
- Inflammation
  - Hematoma formation following by resorption
  - Type III collagen is produced at the injury site by tenocytes.
- Weakest stage of repair
  - Proliferation: maximal type III collagen production
  - Remodeling:
    - Begins at 6 weeks
    - Decreases cellularity
    - Type I collagen predominates
- Two mechanisms:
  - Intrinsic: recruitment of local stem/progenitor cells from endotenon and epitenon
  - Extrinsic: cells from surrounding tissue invade damaged area.
  - Faster but primary source of adhesions

- Achilles, patellar, and supraspinatus tendons are prone to rupture at hypovascular areas.
- Achilles tendon is hypovascular 4–6 cm proximal to calcaneal insertion.
- Responsive to different cytokines and growth factors
  - PDGF genes transfected into tenocytes show collagen formation.
  - VEGF genes transfected into tenocytes show TGF-β upregulation and adhesion formation.
  - When exposed to PMNs (as with inflammation), tenocytes upregulate genes for inflammatory cytokines, TGF-β, and MMPs while suppressing type I collagen expression.

Surgical tendon repairs: weakest at 7–10 days
- Maximum strength achieved at 6 months, reaching two-thirds of original strength.
- No evidence in favor of a trough (exposing tendon to cancellous bone) over direct repair to cortical bone.
- Motion and mechanical loading have beneficial effects on tenocyte function.
- Immobilization decreases strength at tendon-bone interface.

LIGAMENT (see Fig. 1.44)

Characteristics
- Originates and inserts on bone
- Stabilizes joints and prevents displacement of bones
- Contains mechanoreceptors and nerve endings that facilitate joint proprioception
- Like tendon, displays viscoelastic behavior

Structure and composition
- Composition
  - Similar to that of tendon
  - Water: 60%–70% of total weight
  - Collagen: 80% of dry weight
    - 90% type I collagen; also types III, V, VI, XI, and XIV collagen
    - More collagen type I is seen at the origin and insertion, with collagen III seen midsubstance.
  - Elastin (1% dry weight)
  - Proteoglycans (1% dry weight)—function in water retention and contribute to viscoelastic behavior
- Fibroblast
  - Primary cell, oriented longitudinally
  - Functions to synthesize ECM, collagen, and proteoglycans
- Epiligament
  - Similar to that in epitenon; carries the neurovascular and lymphatic supply of tendons
  - Compared with tendon
    - Less total collagen but more type III collagen
    - More proteoglycans and therefore more water
    - Less organized collagen fibers that are more highly cross-linked and intertwined
    - “Uniform microvascularity”—receives supply at insertion site by the epiligamentous plexus
  - Insertion
    - Similar to that of tendon
    - Direct (fibrocartilaginous) insertion
      - Four layers: tendon, fibrocartilage, mineralized fibrocartilage, and bone

FIG. 1.45 (A) India ink specimen demonstrating the vascular supply of the flexor tendons via vincula. (B) Close-up of the specimen. (From Simon SR, editor: Orthopaedic basic science, ed 2, Rosemont, IL, 1994, American Academy of Orthopaedic Surgeons, p 51.)
More common
Deep fibers attach at 90-degree angles
Indirect
Superficial fibers insert into the periosteum and deep fibers insert into bone via Sharpey fibers (perforating calcified collagen fibers).

Injury
• Knee and ankle ligaments are most commonly injured
• Ligaments do not plastically deform.
  • They "break, not bend."
• Midsubstance ligament tears are common in adults.
• Avulsion injuries are more common in children.
• Typically occurs between unmineralized and mineralized fibrocartilage layers

Healing
• Increased number of collagen fibers but
  • Fewer mature cross-links (45% of normal at 1 year)
  • Decrease in mass and diameter
• Three phases, as in bone
  • Inflammatory—early acute mediators (PMNs and then macrophages), with production of type III collagen and growth factors
  • Proliferative—around 1–3 weeks, with replacement of type III collagen by type I collagen (Think of macrophages as weakening the structure—weakest point.)
  • Remodeling and maturation
• Factors that impair ligament healing
  • Intraarticularg ligamentous injury
  • Old age, smoking, NSAID use
  • Diabetes mellitus
  • Alcohol use
  • Local injection of corticosteroids
• Factors that improve ligament healing experimentally
  • Extraarticularg ligamentous injury
  • Compromised immunity
  • IL-10 (antiinflammatory)
  • IL-1 receptor antagonists
  • Mesenchymal stem cells
  • Scaffolds (such as collagen–platelet-rich plasma hydrogels)
  • Mesenchymal stem cells
  • Neuropeptides
  • Calcitonin gene–related peptide

Immobilation
• Adversely affects ligament strength: elastic modulus decreases
• In rabbits, breaking strength reduced dramatically (66%) after 9 weeks of immobilization.
• Effects reverse slowly upon remobilization.
• Prolonged immobilization disrupts collagen structure, which may not return to normal within insertion sites.

Exercise
• Improves mechanical and structural properties
• Increases strength, stiffness, and failure load

NEURAL TISSUE AND INTERVERTEBRAL DISC

• The spine and spinal trauma are covered in Chapters 2, 8, and 11. Peripheral nerve injuries are discussed in Chapter 7.
• Anatomy and physiology of the peripheral nervous system (PNS)
• Neuron (see Fig. 1.49)
  • Cell body (metabolic center; 10% of size of a neuron)
  • Tapers into axon at axon hillock
• Axons: one or more processes that connect the neuron to the spinal cord or end-organ
• Dendrites: processes extending from the cell body that receive signals from surrounding nerve cells
• Myelin sheath
  • Composed primarily of galactocerebroside
  • Speeds wave propagation or conduction (thicker sheath increases conduction speed)
    • Produced by Schwann cells in PNS
    • Schwann cells originate in neural crest and are important in posttraumatic nerve regeneration.
    • Produce nerve growth factor-β, brain-derived growth factor, insulin-like growth factor 1 (IGF-1), and erythropoietin
    • One Schwann cell surrounds a single axon in myelinated fibers
      • Footprint of approximately 100 μm
      • Space between cells is called node of Ranvier (concentrated Na+ channels)
      • Allows for salutatory conduction between nodes of Ranvier
    • One Schwann cell surrounds multiple axons in unmyelinated fibers
• Neurophysiology
  • Axolemma
    • Specialized membrane that surrounds axon and maintains membrane potential
    • Maintains resting potential utilizing Na-K pumps
      • Approximately −70 mV (cell interior has relative negative charge)
  • Action potential (AP)
    • Neurotransmitters cross synapse and trigger opening of Na+ channel.
      • This triggers voltage-gated Na+ channels (responsible for generation of AP) in axon hillock when membrane potential increases to −50 mV.
    • Membrane potential spikes to 30 mV as membrane depolarizes.
    • Potential propagates down axon and triggers voltage-gated Ca2+ channel at axon terminus.
    • Ca2+ enters axon and triggers neurotransmitter release
    • Voltage-gated K+ channels stay open longer than Na+ channels.
      • Leads to hyperpolarization (~75 mV)
    • Propagation faster in myelinated and larger nerves
    • Absolute refractory period
      • Period when voltage-gated Na+ channels cannot be activated
      • Responsible for antegrade propagation of signal
    • Relative refractory period
      • Period when larger than normal stimuli propagate a second AP
      • Result of the hyperpolarization phase of the previous
• Peripheral nerves
  • Highly organized structures composed of nerve fibers, blood vessels, and connective tissues (Fig. 1.46)
  • Nerve fibers vary in size according to function (Table 1.27).
  • Erlanger and Gasser classification
    • Afferent and efferent nerves
    • Uses Roman and Greek letters
Lloyd and Hunt classification
- Only afferent nerves
- Uses Roman numerals
- Can be composed of one fascicle (monofascicular), a few fascicles (oligofascicular), or several fascicles (polyfascicular)
- Axons coated with a fibrous tissue called endoneurium
- Groups of axons (fascicles) covered by perineurium
- Nerve covered by epineurium
  - External epineurium is continuous with dural sleeve of spinal cord.
- Afferent nerves convey information from sensory organ to CNS.
  - Pseudounipolar neuron with cell body in dorsal root ganglia (DRG)
  - Central branch extends away from neuron and travels through spinal cord via dorsal horn.
- Efferent nerves convey information from CNS to periphery.

Unipolar neuron with cell body in ventral horn of spinal cord
- Motor unit: an α-motoneuron and the muscle fibers it innervates
- Internal topography
  - Cross section of nerve changes along length of nerve (divisions, anastomosis, and migration)
  - Fibers within fascicle organized by locations they innervate.
  - Around joints, nerves typically have more and smaller fascicles to accommodate joint motion and decrease risk of injury.
  - Radial nerve at spiral groove has fewer and larger fascicles (higher risk of neurapraxia with humeral fracture)

Sensory receptors (Table 1.28)
- The four attributes of a stimulus are quality, intensity, duration, and location.

Table 1.27  Types and Characteristics of Nerve Fibers

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DIAMETER (MM)</th>
<th>MYELINATION</th>
<th>SPEED</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10–20</td>
<td>Heavy</td>
<td>Fast</td>
<td>Touch</td>
</tr>
<tr>
<td>B</td>
<td>&lt;3</td>
<td>Intermediate</td>
<td>Medium</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>C</td>
<td>&lt;1.3</td>
<td>None</td>
<td>Slow</td>
<td>Pain</td>
</tr>
</tbody>
</table>

Table 1.28 Receptor Types

<table>
<thead>
<tr>
<th>NOCICEPTORS</th>
<th>FIBER</th>
<th>QUALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>Aβ</td>
<td>Sharp, pricking pain</td>
</tr>
<tr>
<td>Thermal</td>
<td>Aγ</td>
<td>Sharp, pricking pain</td>
</tr>
<tr>
<td>Thermal</td>
<td>C</td>
<td>Slow, burning pain</td>
</tr>
<tr>
<td>Polymodal</td>
<td>C</td>
<td>Slow, burning pain</td>
</tr>
</tbody>
</table>

Table 1.29 Summary of Spinal Reflexes

<table>
<thead>
<tr>
<th>SEGMENTAL REFLEX</th>
<th>RECEPTOR ORGAN</th>
<th>AFFERENT FIBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phasic stretch reflex</td>
<td>Muscle spindle (primary endings)</td>
<td>Type Ia (large myelinated)</td>
</tr>
<tr>
<td>Tonic stretch reflex</td>
<td>Muscle spindle (secondary endings)</td>
<td>Type II (intermediate myelinated)</td>
</tr>
<tr>
<td>Clasp-knee response</td>
<td>Muscle spindle (secondary endings)</td>
<td>Type II (intermediate myelinated)</td>
</tr>
<tr>
<td>Flexion withdrawal reflex</td>
<td>Nociceptors (free nerve endings, touch and pressure receptors)</td>
<td>Flexor-reflex afferents: small unmyelinated cutaneous afferents (Aβ, C, and muscle afferent fibers, group III)</td>
</tr>
<tr>
<td>Autogenic inhibition</td>
<td>Golgi tendon organ</td>
<td>Type Ib (large myelinated)</td>
</tr>
</tbody>
</table>

Adapted from Kandel ER et al., editors: Principles of neural science, ed 3, Norwalk, CT, 1991, Appleton & Lange, p 342.


- **Modalities**
  - Nociceptors (pain and temperature)
  - Cutaneous and subcutaneous mechanoreceptors (touch and vibration)
  - Muscle and skeletal mechanoreceptors (proprioception)
- *Spinal cord reflexes (Table 1.29)*
  - These reflexes are “stereotyped responses” to a specific sensory stimulus.

**SECTION 2 ORTHOPAEDIC BIOLOGY**

**CELLULAR AND MOLECULAR BIOLOGY AND IMMUNOLOGY**

- **Chromosomes**
  - 46 chromosomes in 23 pairs: 22 pairs of autosomes, 1 pair of sex chromosomes
  - Composed of DNA coiled around histone proteins
- *DNA has a double-helix structure with linked nucleotides (adenine linked to thymine; guanine linked to cytosine) on a sugar-phosphate backbone*
- *Three nucleotides = 1 codon, which corresponds to one amino acid*
Translation (see Fig. 1.47)
- Building of a protein out of amino acids from mRNA template
- Transfer RNA carries a specific amino acid to the ribosome, based on the mRNA codon.
- Antibodies to tRNA synthetase (anti–Jo-1 antibodies) are seen in dermatomyositis.

Cell cycle and ploidy
- Ploidy is the number of sets of chromosomes in a cell annotated by XN.
- The cell cycle entails the events within a cell that result in DNA duplication, with production of two daughter cells.
  - Growth 0 (G0)—stable phase of cells with diploid (2N) DNA content
  - Growth 1 (G1)—upon stimulus, cells begin growth but remain diploid (2N).
  - Synthesis (S)—period of DNA replication resulting in tetraploidy (4N)
  - Growth 2 (G2)—phase of cell growth and protein synthesis that is tetraploid (4N) throughout
  - Mitosis (M)—sequence of events that result in two identical daughter cells that are each 2N
  - Separation of chromosomal material for daughter cells occurs by spindle fibers’ attachment to centromeres that link sister chromatids
  - Anticentromere antibodies are seen in CREST syndrome.
- Certain proteins regulate progression through the cell cycle. Genetic defects and alterations of these tumor suppressor proteins can predispose a cell to dysregulated growth.
  - Targets E2F, a transcription factor that regulates genes important for cell cycle control.
  - Implicated in retinoblastoma and osteosarcoma
  - p53—prevents entry to S phase
  - Implicated in osteosarcoma, rhabdomyosarcoma, and chondrosarcoma

Genetics

Mendelian inheritance
- Due to transmission of alleles to offspring
  - Phenotype refers to the features (traits) exhibited because of genetic makeup (genotype).
- Mendelian traits may be inherited by one of four modes (Tables 1.30 and 1.31).

Autosomal dominant (AD)
- Involves a gene on an autosomal chromosome; one of the two alleles for the chromosome pair must be abnormal for the disease phenotype to occur.
  - Examples: syndactyly/polydactyly, Marfan syndrome, hereditary multiple exostoses (HME), malignant hyperthermia, Ehlers-Danlos syndrome, achondroplasia, osteogenesis imperfecta (types I and IV)
- Autosomal recessive (AR) (most enzyme/biochemical deficiencies)
  - Involves a gene on an autosomal chromosome; both alleles for the chromosome pair must be abnormal for the disease phenotype to occur.
  - Example: diastrophic dysplasia, due to a mutation in the DTDST (SLC26A2) gene on chromosome 5 that encodes for a sulfate transport protein
- X-linked dominant
### Mendelian Inheritance

<table>
<thead>
<tr>
<th>INHERITANCE PATTERN</th>
<th>DESCRIPTION</th>
<th>PUNNETT SQUARE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal dominant</strong> • A is the mutant dominant allele.</td>
<td>Autosomal dominant disorders typically represent <strong>structural defects</strong>. Disorder is manifested in the heterozygous state (Aa). Affects 50% of offspring (assuming only one parent is affected) Normal offspring do not transmit the condition. There is no gender preference.</td>
<td>![Punnett Square](Aa aa)</td>
</tr>
<tr>
<td><strong>Autosomal recessive</strong> • a is the mutant recessive allele.</td>
<td>Autosomal recessive disorders typically represent <strong>biochemical or enzymatic defects</strong>. Disorder is manifested in the homozygous state (aa). Parents are unaffected (they are most commonly heterozygotes). Affects 25% of offspring (assuming each parent is a heterozygote). There is no gender preference.</td>
<td>![Punnett Square](Aa aa)</td>
</tr>
<tr>
<td><strong>X-linked dominant</strong> • X is the mutant dominant X allele.</td>
<td>X-linked dominant disorders are manifested in the heterozygous state (XʻX or XʻY). Affected female (mating with unaffected male) transmits the X-linked gene to 50% of daughters and 50% of sons. Affected male (mating with unaffected female) transmits the X-linked gene to all daughters and no sons.</td>
<td>![Punnett Square](X' X Y)</td>
</tr>
<tr>
<td><strong>X-linked recessive</strong> • X is the mutant recessive X allele.</td>
<td>Heterozygote (XʻY) male manifests the condition. Heterozygote (XʻX) female is unaffected. Affected male (mating with unaffected female) transmits the X-linked gene to all daughters (who are carriers) and no sons. Carrier female (mating with unaffected male) transmits the X-linked gene to 50% of daughters (who are carriers) and 50% of sons (who are affected).</td>
<td>![Punnett Square](X' X X Y)</td>
</tr>
</tbody>
</table>

### Comprehensive Compilation of Inheritance Pattern, Defect, and Associated Gene in Musculoskeletal Disorders

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>INHERITANCE PATTERN</th>
<th>DEFECT</th>
<th>ASSOCIATED GENE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DYSPLASIAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>Autosomal dominant</td>
<td>Defect in the fibroblast growth factor receptor 3</td>
<td><strong>FGF3R</strong></td>
</tr>
<tr>
<td>Diastrophic dysplasia</td>
<td>Autosomal recessive</td>
<td>Mutation of a gene coding for a sulfate transport protein</td>
<td><strong>DTDST</strong></td>
</tr>
<tr>
<td>Kniest dysplasia</td>
<td>Autosomal dominant</td>
<td>Defect in type II collagen</td>
<td><strong>COL 2A1</strong></td>
</tr>
<tr>
<td>Laron dysplasia (pituitary dwarfism)</td>
<td>Autosomal recessive</td>
<td>Defect in the growth hormone receptor</td>
<td></td>
</tr>
<tr>
<td>McCune-Albright syndrome (polyostotic fibrous dysplasia, café-au-lait spots, precocious puberty)</td>
<td>Sporadic mutation</td>
<td>Germline defect in the Gsα protein</td>
<td>Mutation of Gsα subunit of the receptor/adenylyl cyclase–coupling G proteins</td>
</tr>
<tr>
<td>Metaphyseal chondrodysplasia:</td>
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<tr>
<td>Jansen form</td>
<td>Autosomal dominant</td>
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<tr>
<td>McKusick form</td>
<td>Autosomal recessive</td>
<td></td>
<td><strong>PTH; PTH-related protein</strong> <strong>RMRP</strong></td>
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<tr>
<td>Schmid-tarda form</td>
<td>Autosomal dominant</td>
<td>Defect in type X collagen</td>
<td><strong>COL 10A1</strong></td>
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<tr>
<td>Multiple epiphyseal dysplasia</td>
<td>Autosomal recessive</td>
<td>Cartilage oligomeric matrix protein</td>
<td><strong>COMP</strong></td>
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<tr>
<td>Spondyloepiphysial dysplasia</td>
<td>Autosomal dominant (congenita form)</td>
<td>Defect in type II collagen</td>
<td>Linked to Xp22.12-p22.31, <strong>SEDL</strong> (tarda), and <strong>COL 2A1</strong> (congenita)</td>
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<tr>
<td></td>
<td>X-linked recessive (tarda form)</td>
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<tr>
<td>Achondrogenesis</td>
<td>Autosomal recessive</td>
<td>Fetal cartilage fails to mature</td>
<td><strong>FGF2R</strong></td>
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<tr>
<td>Apert syndrome</td>
<td>Sporadic mutation/autosomal dominant</td>
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<td></td>
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<tr>
<td>Chondrodysplasia punctata</td>
<td>Autosomal dominant</td>
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<tr>
<td>Conradi-Hünerman</td>
<td>Autosomal recessive</td>
<td>Defect in subcellular organelles (peroxisomes)</td>
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<tr>
<td>Rhizomelic form</td>
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<td><strong>CBFA1</strong></td>
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<tr>
<td>Cleidocranial dysplasia (dysostosis)</td>
<td>Autosomal dominant</td>
<td>Mutation of a gene coding for a protein related to osteoblast function</td>
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<tr>
<td>Dysplasia epiphysealis hemimelica (Trevor disease)</td>
<td>Unknown</td>
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<td><strong>EVC</strong></td>
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<tr>
<td>Ellis–van Creveld syndrome (chondro-ectodermal dysplasia)</td>
<td>Autosomal recessive</td>
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<tr>
<td>DISORDER</td>
<td>INHERITANCE PATTERN</td>
<td>DEFECT</td>
<td>ASSOCIATED GENE</td>
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<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Fibrodysplasia ossificans progressiva</td>
<td>Sporadic mutation/autosomal dominant</td>
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<tr>
<td>Geroderma osteodysplastica (Walt Disney dwarfism)</td>
<td>Autosomal recessive</td>
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<tr>
<td>Grebe chondrodysplasia</td>
<td>Autosomal recessive</td>
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<tr>
<td>Hypochondroplasia</td>
<td>Sporadic mutation/autosomal dominant</td>
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<tr>
<td>Kabuki makeup syndrome</td>
<td>Sporadic mutation</td>
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<tr>
<td>Mesomelic dysplasia (Langer type)</td>
<td>Autosomal recessive</td>
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<tr>
<td>Mesomelic dysplasia</td>
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<td>Nievergelt type</td>
<td>Autosomal dominant</td>
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<td>Reinhardt-Pfeiffer type</td>
<td>Autosomal dominant</td>
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<td>Werner type</td>
<td>Autosomal dominant</td>
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<td>Metatrophic dysplasia</td>
<td>Autosomal recessive</td>
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<tr>
<td>Progressive diaphyseal dysplasia (Camurati-Engelmann disease)</td>
<td>Autosomal dominant</td>
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<td>Pseudoachondroplastic dysplasia</td>
<td>Autosomal dominant</td>
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<td>COMP</td>
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<tr>
<td>Pyknody sostosis</td>
<td>Autosomal recessive</td>
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<td>Spondylometaphyseal chondrodysplasia</td>
<td>Autosomal recessive</td>
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<tr>
<td>Spondylothoracic dysplasia (Jarcho-Levin syndrome)</td>
<td>Autosomal recessive</td>
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<td>Thanatophoric dwarfism</td>
<td>Autosomal dominant</td>
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<td>FGF3R</td>
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<tr>
<td>Tooth-and-nail syndrome</td>
<td>Autosomal dominant</td>
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<tr>
<td>Treacher Collins syndrome (mandibulo-facial dysostosis)</td>
<td>Autosomal dominant</td>
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<tr>
<td><strong>METABOLIC BONE DISEASES</strong></td>
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<tr>
<td>Hereditary vitamin D–dependent rickets</td>
<td>Autosomal recessive</td>
<td>See Table 1.16</td>
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<tr>
<td>Hypophosphatasia</td>
<td>Autosomal recessive</td>
<td>See Table 1.16</td>
<td>PHEX</td>
</tr>
<tr>
<td>Hypophosphatemic rickets (vitamin D–resistant rickets)</td>
<td>X-linked recessive</td>
<td>See Table 1.16</td>
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<tr>
<td>Osteogenesis imperfecta</td>
<td>Autosomal dominant (types I and IV)</td>
<td>Defect in type I collagen (abnormal cross-linking)</td>
<td>COL IA1, COL IA2</td>
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<tr>
<td>Albright hereditary osteodystrophy (pseudohyoparathyroidism)</td>
<td>Uncertain</td>
<td>PTH has no effect at the target cells (in the kidney, bone, and intestine)</td>
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<tr>
<td>Infantile cortical hyperostosis (Caffey disease)</td>
<td>Unknown</td>
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<tr>
<td>Ochronosis (alkaptonuria)</td>
<td>Autosomal recessive</td>
<td>Defect in the homogentisic acid oxidase system</td>
<td>CLCN7, TC1RG1</td>
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<tr>
<td>Osteopetrosis</td>
<td>Autosomal dominant (mild, tarda form)</td>
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<td></td>
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<tr>
<td></td>
<td>Autosomal recessive (infan- tile, malignant form)</td>
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<tr>
<td><strong>CONNECTIVE TISSUE DISORDERS</strong></td>
<td></td>
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<tr>
<td>Marfan syndrome</td>
<td>Autosomal dominant</td>
<td>Fibrillin abnormalities (some patients also have type I collagen abnormalities)</td>
<td>FBN1 or TGF-βR2</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome (there are at least 13 varieties)</td>
<td>Autosomal dominant (most common)</td>
<td>Defects in types I and III collagen have been described for some varieties; lysyl oxidase abnormalities</td>
<td>COL 3A1 (for type III; most common) COL 1A2 (for type VII)</td>
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<tr>
<td>Homocystinuria</td>
<td>Autosomal recessive</td>
<td>Deficiency of the enzyme cystathionine β-synthase</td>
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<tr>
<td><strong>MUCOPOLYSACCHARIDOSIS</strong></td>
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<tr>
<td>Hunter syndrome (gargoilism)</td>
<td>X-linked recessive</td>
<td>Deficiency of the enzyme α-L-iduronidase</td>
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<tr>
<td>Hurler syndrome</td>
<td>Autosomal recessive</td>
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<td></td>
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<tr>
<td>Maroteaux-Lamy syndrome</td>
<td>Autosomal recessive</td>
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<td></td>
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<tr>
<td>Morquio syndrome</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
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<tr>
<td>Sanfilippo syndrome</td>
<td>Autosomal recessive</td>
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<td></td>
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<tr>
<td>Scheie syndrome</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
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<tr>
<td><strong>MUSCULAR DYSTROPHIES</strong></td>
<td></td>
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<tr>
<td>Duchenne muscular dystrophy</td>
<td>X-linked recessive</td>
<td>Defect on the short arm of the X chromosome</td>
<td>Dystrophin gene</td>
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<tr>
<td>Becker dystrophy</td>
<td>X-linked recessive</td>
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<td></td>
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<tr>
<td>Fascioscapulohumeral dystrophy</td>
<td>Autosomal dominant</td>
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<tr>
<td>Limb-girdle dystrophy</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
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<tr>
<td>Steinert disease (myotonic dystrophy)</td>
<td>Autosomal dominant</td>
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<tr>
<td>DISORDER</td>
<td>INHERITANCE PATTERN</td>
<td>DEFECT</td>
<td>ASSOCIATED GENE</td>
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<tr>
<td>--------------------------------</td>
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<tr>
<td><strong>HEMATOLOGIC DISORDERS</strong></td>
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<tr>
<td>Hemophilia (A and B)</td>
<td>X-linked recessive</td>
<td>Hemophilia A: factor VIII deficiency</td>
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<tr>
<td></td>
<td></td>
<td>Hemophilia B: factor IX deficiency</td>
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<tr>
<td>Sickle cell anemia</td>
<td>Autosomal recessive</td>
<td>Hemoglobin abnormality (presence of hemoglobin S)</td>
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<tr>
<td>Gaucher disease</td>
<td>Autosomal recessive</td>
<td><strong>Deficient activity of the enzyme β-glucosidase</strong> (glucocerebrosidase)</td>
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<tr>
<td>Hemochromatosis</td>
<td>Autosomal recessive</td>
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<tr>
<td>Niemann-Pick disease</td>
<td>Autosomal recessive</td>
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<td></td>
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<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>Uncertain</td>
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<tr>
<td>Thalassemia</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
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<tr>
<td>von Willebrand disease</td>
<td>Autosomal dominant</td>
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<tr>
<td><strong>CHROMOSOMAL DISORDERS WITH MUSCULOSKELETAL ABNORMALITIES</strong></td>
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<tr>
<td>Down syndrome</td>
<td></td>
<td>Trisomy of chromosome 21</td>
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<tr>
<td>Angelman syndrome</td>
<td></td>
<td>Chromosome 15 abnormality</td>
<td>Associated with many genetic anomalies, including trisomy of chromosomes 8 and 21</td>
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<tr>
<td>Clinodactyly</td>
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<tr>
<td>Edward syndrome</td>
<td>X-linked trait (does not follow the typical pattern of an X-linked trait)</td>
<td>Trisomy of chromosome 18</td>
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<tr>
<td>Fragile X syndrome</td>
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<tr>
<td>Klinefelter syndrome (XXY)</td>
<td></td>
<td>An extra X chromosome in affected boys and men</td>
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<tr>
<td>Langer-Giedion syndrome</td>
<td>Sporadic mutation</td>
<td>Chromosome 8 abnormality</td>
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<tr>
<td>Nail-patella syndrome</td>
<td>Autosomal dominant</td>
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<td></td>
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<tr>
<td>Patau syndrome</td>
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<tr>
<td>Turner syndrome (XO)</td>
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<tr>
<td><strong>NEUROLOGIC DISORDERS</strong></td>
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<tr>
<td>Charcot-Marie-Tooth disease</td>
<td>Autosomal dominant</td>
<td><strong>Chromosome 17 defect for encoding peripheral myelin protein-22</strong></td>
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<tr>
<td>Congenital insensitivity to pain</td>
<td>Autosomal recessive</td>
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<td>Dejerine-Sottas disease</td>
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<td>Friedreich ataxia</td>
<td>Autosomal recessive</td>
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<td>Huntington disease</td>
<td>Autosomal recessive</td>
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<tr>
<td>Menkes syndrome</td>
<td>X-linked recessive</td>
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<td>Pelizaeus-Merzbacher disease</td>
<td>X-linked recessive</td>
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<td>Riley-Day syndrome</td>
<td>Autosomal recessive</td>
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<td>Spinal muscular atrophy (Werndig-Hoffman disease and Kugelberg-Welander disease)</td>
<td>Autosomal recessive</td>
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<tr>
<td>Sturge-Weber syndrome</td>
<td>Sporadic mutation</td>
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<tr>
<td>Tay-Sachs disease</td>
<td>Autosomal recessive</td>
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<tr>
<td><strong>DISEASES ASSOCIATED WITH NEOPLASIAS</strong></td>
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<tr>
<td>Ewing sarcoma</td>
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<td></td>
<td>11;22 chromosomal translocation (EWS/FL11 fusion gene)</td>
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<tr>
<td>Multiple endocrine neoplasia (MEN):</td>
<td>Autosomal dominant</td>
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<td></td>
</tr>
<tr>
<td>Type I</td>
<td>Autosomal dominant</td>
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<tr>
<td>Type II</td>
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<td>Type III</td>
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<tr>
<td>Neurofibromatosis (von Recklinghausen disease) type 1 (NF1) and type 2 (NF2)</td>
<td>Autosomal dominant</td>
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<tr>
<td>Synovial sarcoma</td>
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<tr>
<td><strong>MISCELLANEOUS DISORDERS</strong></td>
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<tr>
<td>Malignant hyperthermia</td>
<td>Autosomal dominant</td>
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<td>Osteochondromatosis</td>
<td>Autosomal dominant</td>
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<tr>
<td>Postaxial polydactyly</td>
<td>Autosomal dominant</td>
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<tr>
<td>Camptodactyly</td>
<td>Autosomal dominant</td>
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<tr>
<th>DISORDER</th>
<th>INHERITANCE PATTERN</th>
<th>DEFECT</th>
<th>ASSOCIATED GENE</th>
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<tbody>
<tr>
<td>Cerebrooculofacioskeletal syndrome</td>
<td>Autosomal recessive</td>
<td>Fibrillin gene (chromosome 5)</td>
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<tr>
<td>Congenital contractual arachnodactyly</td>
<td>Autosomal dominant</td>
<td>Fibrillin gene (chromosome 5)</td>
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<td>Distal arthrogryposis syndrome</td>
<td>Autosomal dominant</td>
<td>Fibrillin gene (chromosome 5)</td>
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<td>Dupuytren contracture</td>
<td>Autosomal recessive</td>
<td>Fibrillin gene (chromosome 5)</td>
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<tr>
<td>Fabry disease</td>
<td>X-linked recessive</td>
<td>Deficiency of α-galactosidase A</td>
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<td>Fanconi pancytopenia</td>
<td>Autosomal recessive</td>
<td>Deficiency of α-galactosidase A</td>
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<tr>
<td>Freeman-Sheldon syndrome (cranio-carpotarsal dysplasia; whistling face syndrome)</td>
<td>Autosomal recessive</td>
<td>Fibrillin gene (chromosome 5)</td>
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<td>GM1 gangliosidosis</td>
<td>Autosomal recessive</td>
<td>Fibrillin gene (chromosome 5)</td>
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<td>Hereditary anonychia</td>
<td>Autosomal dominant</td>
<td>Fibrillin gene (chromosome 5)</td>
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<td>Holt-Oram syndrome</td>
<td>Autosomal dominant</td>
<td>Fibrillin gene (chromosome 5)</td>
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<td>Humeroradial synostosis</td>
<td>Autosomal recessive</td>
<td>Fibrillin gene (chromosome 5)</td>
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<td>Klippel-Feil syndrome</td>
<td>Faulty development of spinal segments along the embry-onic neural tube</td>
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<td>Klippel-Trénaunay-Weber syndrome</td>
<td>Sporadic mutation</td>
<td>Deficiency of galactocerebroside β-galactosidase</td>
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<td>Larsen syndrome</td>
<td>Autosomal dominant</td>
<td>Absence of the enzyme hypoxanthine guanine phosphoribosyl transferase</td>
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<td>Lesch-Nyhan disease</td>
<td>X-linked trait</td>
<td>Absence of the enzyme hypoxanthine guanine phosphoribosyl transferase</td>
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<tr>
<td>Madelung deformity</td>
<td>Autosomal dominant</td>
<td>Deficiency of the enzyme α-mannosidase</td>
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<td>Mannosidosis</td>
<td>Autosomal recessive</td>
<td>Deficiency of the enzyme α-mannosidase</td>
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<td>Maple syrup urine disease</td>
<td>Autosomal recessive</td>
<td>Deficiency of the enzyme α-mannosidase</td>
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<td>Meckel syndrome (Gruber syndrome)</td>
<td>Autosomal recessive</td>
<td>Deficiency of the enzyme α-mannosidase</td>
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<td>Möbius syndrome</td>
<td>Autosomal recessive</td>
<td>Deficiency of the enzyme α-mannosidase</td>
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<td>Mucolipidosis (oligosaccharidosis)</td>
<td>Autosomal recessive</td>
<td>Deficiency of the enzyme α-mannosidase</td>
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<tr>
<td>Multiple exostoses</td>
<td>Autosomal dominant</td>
<td>A family of enzyme deficiency diseases</td>
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</tr>
<tr>
<td>Multiple pterygium syndrome</td>
<td>Autosomal recessive</td>
<td>A family of enzyme deficiency diseases</td>
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<tr>
<td>Noonan syndrome</td>
<td>Sporadic mutation</td>
<td>A family of enzyme deficiency diseases</td>
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<tr>
<td>Oral-facial-digital (OFD) syndrome</td>
<td>Autosomal dominant</td>
<td>A family of enzyme deficiency diseases</td>
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<tr>
<td>Osler-Weber-Rendu syndrome (he-reditary hemorrhagic telangiectasia)</td>
<td>Autosomal dominant</td>
<td>A family of enzyme deficiency diseases</td>
<td></td>
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<tr>
<td>Pfeiffer syndrome (acrocephalosyn-dactyly)</td>
<td>Sporadic mutation/autosomal dominant</td>
<td>Enzyme deficiency characterized by the inability to convert phenylalanine to tyrosine because of a chromosome 12 abnormality</td>
<td></td>
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<tr>
<td>Phenylketonuria</td>
<td>Autosomal recessive</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
<td></td>
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<tr>
<td>Phytanic acid storage disease</td>
<td>Autosomal recessive</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
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<td>Progeria (Hutchinson-Gilford progeria syndrome)</td>
<td>Autosomal dominant</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
<td></td>
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<tr>
<td>Proteus syndrome</td>
<td>Autosomal dominant</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
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<td>Prune-belly syndrome</td>
<td>Autosomal dominant</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
<td></td>
</tr>
<tr>
<td>Radioulnar synostosis</td>
<td>Sporadic mutation/X-linked dominant</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
<td></td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>Autosomal recessive</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
<td></td>
</tr>
<tr>
<td>Roberts syndrome (pseudothalidomide syndrome)</td>
<td>Sporadic mutation/autosomal recessive</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
<td></td>
</tr>
<tr>
<td>Russell-Silver syndrome</td>
<td>Sporadic mutation (possibly X-linked)</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
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<tr>
<td>Saethre-Chotzen syndrome</td>
<td>Autosomal dominant</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
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<tr>
<td>Sandhoff disease</td>
<td>Autosomal recessive</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
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<tr>
<td>Schwartz-Jampel syndrome</td>
<td>Autosomal dominant</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
<td></td>
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<tr>
<td>Seckel syndrome (so-called bird-headed dwarfism)</td>
<td>Autosomal recessive</td>
<td>ENTH3: greater burden of disease and risk of malignancy</td>
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Table 1.31 Comprehensive Compilation of Inheritance Pattern, Defect, and Associated Gene in Musculoskeletal Disorders—cont’d

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>INHERITANCE PATTERN</th>
<th>DEFECT</th>
<th>ASSOCIATED GENE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stickler syndrome (hereditary progres-</td>
<td>Autosomal dominant</td>
<td>Collagen abnormality</td>
<td></td>
</tr>
<tr>
<td>sive arthroophthalmopathy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia-aplasia of radius (TAR)</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
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<tr>
<td>syndrome</td>
<td></td>
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<tr>
<td>Tarsal coalition</td>
<td>Autosomal dominant</td>
<td></td>
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<tr>
<td>Trichohiphosphalangeal syndrome</td>
<td>Autosomal dominant</td>
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<tr>
<td>Argininemia</td>
<td>Autosomal recessive</td>
<td></td>
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<tr>
<td>Argininosuccinic aciduria</td>
<td>Autosomal recessive</td>
<td></td>
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<tr>
<td>Citrullinemia</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ornithine transcarbamylase deficiency</td>
<td>X-linked</td>
<td></td>
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<tr>
<td>VATER association</td>
<td>Sporadic mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zygodactyly</td>
<td>Autosomal dominant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Example: hypophosphatemic rickets, due to PHEx gene mutation (Xp.22)
- X-linked recessive
  - Examples: Duchenne and Becker muscular dystrophies, Hunter syndrome, hemophilia, spondyloepiphyseal dysplasia (SED) tarda

Nonmendelian traits may be inherited through “polygenic” transmission caused by the action of several genes
- Charcot-Marie-Tooth disease (AD, AR, and X-linked forms)
- Osteopetrosis (AD and AR)
- Osteogenesis imperfecta (AD and AR)
- Neurofibromatosis (AD and AR)
- SED (AD and X-linked)

- Mutations
  - Genetic disorders arise from alterations (mutations) in the genetic material.
  - Most skeletal dysplasias are single-gene mutations.
    - Collagen type I (bone) defects
    - Osteogenesis imperfecta (types I–IV)—COL1A1 and COL1A2 genes
    - Ehlers-Danlos—COL5A1 and COL5A2 genes
    - Collagen type II (cartilage) defects
    - SED—COL2A1 gene, usually random mutations
  - Others
    - Multiple epiphyseal dysplasia—COMP (cartilage oligomeric matrix protein) gene; also associated with pseudoachondroplasia
    - Marfan syndrome—FBN1 (fibrillin-1) gene
    - Achondroplasia—FGFR3 (fibroblast growth factor receptor) gene
    - Spinal muscular atrophy—SMN1 (survival motor neuron-1) gene

- Epigenetics
  - Genetic alterations that are not caused by mutations in DNA sequence
  - DNA methylation
  - Histone posttranslational modifications
  - Genomic imprinting (parent-of-origin phenotypes)
    - An example of genomic imprinting is the loss of a region in chromosome 15 with Prader-Willi syndrome (paternal; obesity, hypogonadism, hypotonia) and Angelman syndrome (maternal; epilepsy, tremors, smiling).

Chromosomal abnormalities
- Disruptions in the normal arrangement or number of chromosomes
- Trisomy: one chromosome pair has an extra chromosome (total: 47 chromosomes)
  - Trisomy 21 (Down syndrome)—ligamentous laxity, atlantoaxial instability, patellar and hip dislocations, severe flatfoot, and bunions
- Deletion: absence of a section of one chromosome (in a chromosome pair).
- Duplication: presence of an extra section of one chromosome (in a chromosome pair).
- Translocation: exchange of a portion of one chromosome with a portion of another chromosome
- Inversion: a broken portion of a chromosome reattaches to the same chromosome in the same location but in a reverse direction.

Genetics of musculoskeletal conditions and abnormalities are summarized in Table 1.31.

Techniques used to study genetic (inherited) disorders
- Restriction enzymes
  - Used to cut DNA at precise, reproducible cleavage locations
  - Identify polymorphisms (alternative gene expressions)
- Agarose gel electrophoresis
  - Molecules are suspended in agarose gel that is exposed to an electric field.
  - Molecules move through the gel according to size and polarity
- Southern blot: detects DNA
- Northern blot: detects RNA
- Western blot: detects protein

Plasmid vectors
- A plasmid is a small, extrachromosomal, circular piece of DNA that replicates independently of the host DNA. Plasmids can confer antibiotic resistance between bacteria.
- The recombinant plasmid is inserted into a bacterium (the vector) by a process called transformation. The bacterium then produces a recombinant protein encoded by the inserted gene.

Cytogenetic analysis

TGF-βR2, TGF-β receptor 2; VATER, vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.
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Gross examination of chromosomes under microscope with the use of techniques of banding and fluorescent in situ hybridization

- **Used to detect chromosomal translocations**
  - t(X;18)—in synovial sarcoma
  - t(11;22)—in Ewing sarcoma
  - t(2;13)—in rhabdomyosarcoma
  - t(12;16)—in myxoid liposarcoma
  - t(12;22)—in clear cell sarcoma

- Transgenic animals
  - Bred to investigate the function of cloned genes.

- PCR amplification
  - Repetitive synthesis (amplification) of a specific DNA sequence in vitro
  - Screening DNA for gene mutations (e.g., prenatal diagnosis of sickle cell)

- Reverse transcription PCR (RT-PCR)
  - Reverse transcriptase is used to “reverse transcribe” RNA to complementary DNA.
  - Typically used to study RNA viruses

- Silencing RNA (siRNA)
  - Blocks transcription of mRNA in order to study result of gene’s loss of function

### Immunology

- The immune system is broadly categorized into two branches: the innate and the adaptive, with interaction and overlap between the two (Fig. 1.48).

- The **innate system** is primitive, nonspecific, the first line of defense using complement and leukocytes.
  - Is antigen independent and involves **NK cells**, mast cells, basophils, eosinophils, macrophages, neutrophils, and dendritic cells
  - Barriers—physical and chemical components (e.g., enzymes, pH)
    - Skin—sebum, sweat (lysozyme, RNases and DNases, defensins, cathelicidins)
    - Mucous membranes (IgA is most common immunoglobulin)
    - Respiratory epithelium
  - **Transgenic animals**
  - Bred to investigate the function of cloned genes.
  - **PCR amplification**
    - Repetitive synthesis (amplification) of a specific DNA sequence in vitro
    - Screening DNA for gene mutations (e.g., prenatal diagnosis of sickle cell)
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- **Complement**
  - Activated by IgM or IgG antigen (Ag) complexes, microbial products, or mannose on microorganisms
  - Mediates chemotaxis of PMNs, opsonization (tagging of evasive bacteria for elimination in the spleen), and membrane attack complex lysis of microbes, among other functions
  - **The adaptive system** is more complex, is antigen dependent, and works through antigen presentation with B and T lymphocytes and antibodies.
  - Response to a pathogen generates an immunologic memory in the adaptive system.

- **Urinary tract**
  - Recognition of pathogens by innate system
  - **Pathogen-associated molecular patterns** (PAMPs) on microbes are recognized by TLRs on innate immune system cells (e.g., macrophages and dendritic cells).
  - Example of a PAMP is bacterial lipopolysaccharide (LPS), which is recognized by TLR-4.
  - There is an upregulation of NF-κB transcription factor, resulting in release of immune mediators (e.g., IL-1, IL-6, TNF-α).
  - IL-6 causes the liver to release inflammatory mediators such as CRP.
  - Arachidonic acid released from cell membranes is acted on by COX and 5-lipoxygenase to make prostaglandins and leukotrienes that mediate exudation, chemotaxis, and bronchospasm.
  - **Ibuprofen inhibits COX and reduces prostaglandin production, preventing renal efferent arteriolar relaxation and increasing GFR.**
  - **Factor (XII)—inflammatory protein made in the liver**
  - When exposed to collagen under damaged endothelium, activates coagulation
  - Acute production of coagulation factors elevates ESR.

- **Immune response**
  - Response to a pathogen generates an immunologic memory in the adaptive system.

### FIG. 1.48 Innate immunity and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. (From Abbas AK et al: *Cellular and molecular immunology*, ed 6, Philadelphia, 2009, Saunders.)
• Antigens are ligands recognized by the immune system. The smallest part of an antigen “seen” by a T- or B-cell receptor is an epitope.
• Cell mediated—T lymphocytes (helper, CD4+; cytotoxic, CD8+), macrophages
• Targets intracellular bacteria, virus, fungi, parasites, tumors, and transplanted organs/orthopaedic hardware
• Antigen-presenting cells (APCs—macrophages, dendritic cells, certain B cells, and Langerhans cells) process antigens.
• Humoral—B lymphocytes and their matured counterparts, plasma cells. Both produce antibodies.
• Targets exotoxin-mediated disease, encapsulated bacterial infection, other viral infections
• Each B cell makes antibodies specific to one single epitope (antigen). B cells use immunoglobulins (IgM and IgD) as cell membrane receptors.
• Terminally differentiated B cells are called plasma cells. The difference is that they secrete immunoglobulins into fluid.
• Immunoglobulins (Fig. 1.49) (mnemonic: MADGE)
  • IgM: heaviest, first in the adaptive response
  • IgA: in mucosal surfaces (e.g., MALT [mucosa-associated lymphoid tissue]) and secretions
  • IgD: only on B-cell surfaces
  • IgG: also on B-cell surface but also secreted. Mediates opsonization; later in the adaptive response
  • IgE: on the surface of mast cells (allergic reactions), basophils, and eosinophils (response to parasite).

Once secreted, antibodies can defend by a variety of mechanisms.
• Neutralization of viruses and toxins
• Opsonization
• Complement activation (IgG and IgM)
• Antibody cellular cytotoxicity
• Prevention of adherence and colonization (IgA)
• Cellular response in inflammation
• Neutrophil response—first cells recruited to sites of tissue injury
• Margination, rolling, adhesion, chemotaxis, and phagocytosis
• Macrophage response—follows neutrophil response
• Initiate inflammatory response in osteolysis or aseptic loosening (occurs in response to particles <1 μm in diameter)
• Mast cells—activated by trauma, complement, or IgE cross-linking, releasing histamine granules
• Histamine mediates the peripheral nerve axon reflex that results in vascular smooth muscle relaxation.
• Excessive endothelial vasodilation with respiratory smooth muscle constriction is an emergency mediated by IgE-type I hypersensitivity reaction and can lead to shock and death.

Autoimmunity
• Recognition of epitopes from the “self”
  • ANAs, which are seen in many disease processes
    • Anti-Sm—SLE
    • Anti-RNP—mixed connective tissue disease
    • Anti–scl-70—scleroderma
    • Anti–dsDNA—SLE; also implicated in SLE nephritis
    • Antihistone—drug-induced lupus
    • Anti-Ro and Anti-La—Sjögren syndrome
• HLA gene on chromosome 6 can be rearranged to make an antigen-specific receptor on APCs for up to 10^15 different epitopes.
• HLA-B27 is associated with a variety of rheumatologic diseases (mnemonic: PAIR)
  • Psoriatic arthritis
  • AS
  • Inflammatory bowel disease
  • Reactive arthritis (Reiter syndrome)
  • Also juvenile RA
• HLA-DR3: myasthenia gravis and SLE
• HLA-DR4: RA

Hypersensitivity reactions
• Type I: mediated by IgE
  • Anaphylaxis or allergic response, immediate response, mast cell degranulation
  • Food allergy (milk, egg, peanut, seafood, etc.) and drug allergies
• Type II: mediated by IgG or IgM, cytotoxic, antibody-mediated response
  • Heparin-induced thrombocytopenia
  • Rheumatic fever
  • Myasthenia gravis
• Type III: immune complex mediated (antigen-antibody [e.g., IgG-Ag])
  • SLE
  • RA

![Basic subunit structure of the immunoglobulin molecule.](https://example.com/image.png)
INFECTION AND MICROBIOLOGY

Musculoskeletal infections overview

Musculoskeletal infections overview

Type IV: cell-mediated (no antibodies); helper T cells activate cytotoxic cells and macrophages to attack tissue; delayed response.

- TB screening with PPD (purified protein derivative)/ Mantoux test
- Type 1 diabetes mellitus
- Multiple sclerosis
- Type IV response to metallic orthopaedic implants
  - Pseudotumor hypersensitivity response can occur years after THA.

Cytokines

- Low-molecular-weight proteins that bind to receptors and elicit cellular responses.
- Each cytokine can serve a variety of functions:
  - IL-1—initiates acute phase response
  - IL-6 is key to growth and survival of multiple myeloma (MM) cells.
    - Generated in autocrine (MM cells) and paracrine (bone marrow stromal cells and osteoblasts) fashion
  - IL-10—antiinflammatory
  - TNF-α—helps mediate inflammatory response to intracellular infections
  - TGF-β—limits inflammation and promotes fibrosis

Staphylococcus: roughly 80% of orthopaedic infections

- Antibiotic resistance
  - Penicillin (β-lactam antibiotic)—inhibits peptidoglycan bonds of bacterial cell wall
  - β-Lactamases are enzymes produced by bacteria that provide resistance by breaking down the antibiotic structure.
- MRSA
  - mecA gene
    - Located on staphylococcal chromosome cassette mobile element—carrying IV (SCCmecIV)
    - Encodes for penicillin-binding protein 2A, which has a low affinity for β-lactam antibiotics
- Community versus hospital
  - Hospital-acquired MRSA (HA-MRSA) or health care–acquired (HC-MRSA)
  - Seen in patients from nursing homes, those with recent bacteria have larger SCCmec genetic elements
    - Multiple antibiotic resistance genes
    - More drug resistance; known as “super bugs”
  - Community-acquired MRSA (CA-MRSA)
    - Bacteria have smaller SCCmec genetic elements
    - Less drug resistance
    - Almost all have PVL cytotoxin
    - γ-Hemolysin: a pore-forming toxin that can lyse PMNs

Streptococcus:

- TSS toxin-1 causes toxic shock syndrome
  - Acute febrile illness with a generalized scarlatiniform rash
  - Hypotension (shock) with organ system failure
  - Desquamation of palmar/plantar skin lesions (if the patient lives)
- Treatment:
  - Removal of foreign object (retained sponge or tampon)
  - Supportive care with fluids and anti-Staphylococcus antibiotics

Superantigens

- Activate approximately 20% of T cells
- Trigger cytokine release
- Systemic inflammation; appears as septic shock
  - S. pyogenes (group A streptococci): M protein
  - S. aureus: TSS toxin-1 causes toxic shock syndrome
  - Acute febrile illness with a generalized scarlatiniform rash
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  - Supportive care with fluids and anti-Staphylococcus antibiotics
Basic Sciences

Infection by tissue type

Soft tissue infections: superficial to deep (Table 1.32)

- **Erysipelas**: infection of dermis and lymphatics—group A streptococci
  - Painful raised lesion with a red, edematous, indurated (peau d’orange) appearance and an advancing raised border
  - Treatment: penicillins or erythromycin

- **Cellulitis**: subcutaneous infection most commonly group A streptococci or *S. aureus*
  - Acute spreading infection with pain, erythema, and warmth; with or without lymphadenopathy; may develop into abscess (may surround abscess or ulcer)
  - Treatment: routine for cellulitis—penicillin, dicloxacillin; but IV cefazolin or nafcillin if systemic systems prominent or patient is at high risk (asplenia, neutropenia, immunocompromise, cirrhosis, cardiac or renal failure, local trauma, or preexisting edema)

- **Abscess**: pus-filled inflammatory subcutaneous nodule (furuncle = “boil”) that may be multiple and may coalesce (carbuncle): almost always *S. aureus*. Small lesions sometimes mistaken as spider bites.
  - Painful pus under pressure
  - Treatment: incision and drainage (I&D), then left open, with culture and sensitivity testing to select antibiotics.
  - For simple abscesses, addition of systemic antibiotics has not been shown to improve cure rate or decrease recurrence above I&D alone.
  - Systemic antibiotics only for (Infectious Disease Society of America Guidelines):
    - Severe or extensive disease
    - Rapid progression in the presence of associated cellulitis
    - Signs and symptoms of systemic illness
    - Associated comorbidities or immunosuppression, extremes of age
    - Abscess in an area difficult to drain
    - Associated septic phlebitis
  - Lack of response to incision and drainage
  - Empirical antibiotics selected should aim at MRSA.

- Necrotizing fasciitis
  - Rare, rapidly progressive, life-threatening infection of the fascia and subcutaneous tissue
  - Causes liquefactive necrosis with thrombosis of the cutaneous microcirculation
  - **Most commonly polymicrobial**, but group A β-hemolytic ("flesh-eating") streptococci the most common monomicrobial cause (i.e., *S. pyogenes*).
  - Risk factors: diabetes, peripheral vascular disease, liver failure
  - Death most related to delay in treatment for more than 24 hours
  - Fascial infection spreads faster than the observed skin changes.

- Skin microcirculation thrombosis and later necrosis
  - Early—pain out of proportion, swelling and edema
  - Late
    - Blisters/bullae
    - Skin that does not blanch (skin is dying)
    - Skin becomes numb (nerves are dying)
  - Difficult diagnosis—paucity of cutaneous findings so high clinical suspicion needed
  - Less than one-fifth of cases diagnosed at admission; preadmission antibiotics mask severity
  - Repeated examinations noting margins that migrate quickly despite antibiotic treatment

- Surgical findings
  - Grayish necrotic fascia
  - Lack of normal muscular fascial resistance to blunt dissection
  - Lack of bleeding of the fascia during dissection
  - Foul-smelling “dishwater” pus
  - Treatment: broad-spectrum antibiotics
    - Early operative débridement of all necrotic tissue—level selected should be ahead of the infection
    - Amputation/disarticulation should be considered.
    - Second-look procedure should be performed 24 hours later for reevaluation.

- Gas gangrene
  - *C. perfringens* (obligate anaerobe) most common organism that produces gas and toxins in subcutaneous tissues and muscle
  - Dirty wound managed with primary closure: war wounds, tornado, lawn mower
  - Inadequate débridement of more severe devitalizing injuries
  - Clostridial dermonecrotizing exotoxin lecithinase
  - Crepitation of soft tissue, air in soft tissues on x-rays, foul “sweet”-smelling discharge
  - Treatment
    - Early, adequate, and thorough surgical débridement
    - Delayed closure and second-look procedure 24 hours later for reevaluation
    - High-dose IV penicillin and hyperbaric oxygen can help if available.
  - Surgical site infection
  - Infections are the product of bacteria that take hold in a favorable wound environment in a host with a susceptible immune system.

- Bacterial issues
  - Load
    - More than 10^5 colony-forming units (CFUs) needed in normal host to cause infection
    - Need only about 100 CFUs if foreign object present
  - Prevention
    - Prophylactic antibiotics
      - Given from less than 1 hour before until 24 hours after procedure
      - Repeated if preceding time is more than 4 hours (longer than half-life of antibiotic selected)
      - Repeated if blood loss more than 1000 mL
      - Doubled if patient weighs more than 80 kg (>176 lb)
    - Avoidance of hematogenous seeding
      - No active infections in elective cases—legs, feet, toes checked preoperatively
<table>
<thead>
<tr>
<th>Type</th>
<th>Affected Tissues</th>
<th>Clinical Findings</th>
<th>Organisms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis, erysipelas</td>
<td>Superficial, subcutaneous</td>
<td>Erythema; tenderness; warmth; lymphangitis; lymphadenopathy</td>
<td>Group A streptococci (most common) Staphylococcus aureus (less common)</td>
<td>Initial antibiotic treatment: penicillin G or penicillinase-resistant synthetic penicillins (nafcillin or oxacillin) Alternative therapies: erythromycin, first-generation cephalosporins, amoxicillin/clavulanate, azithromycin, clarithromycin, tigecycline, or daptomycin</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>Muscle fascia</td>
<td>Aggressive, life-threatening; may be associated with an underlying vascular disease (particularly diabetes) Commonly occurs after surgery, trauma, or streptococcal skin infection</td>
<td>Four types: Groups A, C, and G streptococci Clostridia Polymicrobial (aerobic plus anaerobic) MRSA</td>
<td>Extensive emergency surgical débridement (involving entire length of the overlying cellulitis) and intravenous antibiotics Initial antibiotic treatments: penicillin G for streptococcal or clostridial infection; imipenem, doripenem, or meropenem for polymicrobial infections Add vancomycin or daptomycin if MRSA suspected Primary treatment: surgical (radical) débridement with fasciotoxins Hyperbaric oxygen may be a useful adjuvant therapy, although its effectiveness remains inconclusive Initial antibiotic treatment: clindamycin plus penicillin G Alternative therapies include ceftriaxone or erythromycin</td>
</tr>
<tr>
<td>Gas gangrene</td>
<td>Muscle; commonly in grossly contaminated, traumatic wounds, particularly those that are closed primarily</td>
<td>Progressive, severe pain; edema (distant from the wound); foul-smelling, serosanguineous discharge; high fever; chills; tachycardia; confusion Clinical findings consistent with toxemia Radiographs typically show widespread gas in the soft tissues (facilitates rapid spread of the infection)</td>
<td>Classically caused by Clostridium perfringens, Clostridium septicum, or other histotoxic Clostridium spp. These gram-positive, anaerobic, spore-forming rods produce exotoxins that cause necrosis of fat and muscle and thrombosis of local vessels</td>
<td>Primary treatment: surgical (radical) débridement with fasciotomies Hyperbaric oxygen may be a useful adjuvant therapy, although its effectiveness remains inconclusive Initial antibiotic treatment: clindamycin plus penicillin G Alternative therapies include ceftriaxone or erythromycin</td>
</tr>
<tr>
<td>Tox shock syndrome:</td>
<td>Toxemia, not septicemia</td>
<td>Fever, hypotension, an erythematous macular rash with a serous exudate (gram-positive cocci are present) The infected wound may look benign, which may belie the seriousness of the underlying condition</td>
<td>Caused by toxins produced by S. aureus</td>
<td>Irrigation and débridement and intravenous antibiotics with intravenous immune globulin Initial antibiotic treatment: penicillinase-resistant penicillins (nafcillin or oxacillin), vancomycin if MRSA Alternative therapies include first-generation cephalosporins Patients may also require emergency fluid resuscitation</td>
</tr>
<tr>
<td>Staphylococcal</td>
<td>Toxemia, not septicemia</td>
<td>Similar to staphylococcal TSS</td>
<td>Toxins from group A, B, C, or G Streptococcus pyogenes</td>
<td>Initial antibiotic treatment: clindamycin plus penicillin G Alternative therapy includes ceftriaxone or clindamycin Intravenous immune globulin may be used; associated with decrease in organ failure, but no effect on all-cause mortality in children Initial antibiotic treatment: trimethoprim-sulamethoxazole or clindamycin MRSA species are best treated with vancomycin (alternatives for MRSA include daptomycin and cefotiboprole)</td>
</tr>
<tr>
<td>Streptococcal</td>
<td>Toxemia, not septicemia</td>
<td>Similar to staphylococcal TSS</td>
<td>S. aureus; groups A, B, C, and G streptococci Other organism may be involved</td>
<td>Initial antibiotic treatment: clindamycin plus penicillin G Alternative therapy includes ceftriaxone or clindamycin Intravenous immune globulin may be used; associated with decrease in organ failure, but no effect on all-cause mortality in children Initial antibiotic treatment: trimethoprim-sulamethoxazole or clindamycin MRSA species are best treated with vancomycin (alternatives for MRSA include daptomycin and cefotiboprole)</td>
</tr>
<tr>
<td>Surgical wound infection</td>
<td>Varies</td>
<td>Similar to staphylococcal TSS</td>
<td>Toxins from group A, B, C, or G Streptococcus pyogenes</td>
<td>Initial antibiotic treatment: clindamycin plus penicillin G Alternative therapy includes ceftriaxone or clindamycin Intravenous immune globulin may be used; associated with decrease in organ failure, but no effect on all-cause mortality in children Initial antibiotic treatment: trimethoprim-sulamethoxazole or clindamycin MRSA species are best treated with vancomycin (alternatives for MRSA include daptomycin and cefotiboprole)</td>
</tr>
<tr>
<td>Marine injuries</td>
<td>Varies</td>
<td>History of fishing (or other marine activity) injury, with signs of infection Culture specimens at 30°C (60°F); organisms may take several weeks to grow on culture media</td>
<td>Marine injuries involve organisms that can cause indolent infections Vibrio vulnificus is the most likely organism in infected wounds that were exposed to brackish water or shellfish; can cause a devastating infection Atypical mycobacteria (e.g., Mycobacterium marinum) should also be considered for injuries with indolent, low-grade infection</td>
<td>Initial antibiotic treatment: penicillin G or penicillinase-resistant synthetic penicillins (nafcillin or oxacillin) Alternative therapies: erythromycin, first-generation cephalosporins, amoxicillin/clavulanate, azithromycin, clarithromycin, tigecycline, or daptomycin Extensive emergency surgical débridement (involving entire length of the overlying cellulitis) and intravenous antibiotics Initial antibiotic treatments: penicillin G for streptococcal or clostridial infection; imipenem, doripenem, or meropenem for polymicrobial infections Add vancomycin or daptomycin if MRSA suspected Primary treatment: surgical (radical) débridement with fasciotomies Hyperbaric oxygen may be a useful adjuvant therapy, although its effectiveness remains inconclusive Initial antibiotic treatment: clindamycin plus penicillin G Alternative therapies include ceftriaxone or erythromycin</td>
</tr>
</tbody>
</table>
Bite infections (Consider delayed primary closure at 48–72 hours)

- Use vancomycin 1 g every 12 hours
- 2% intranasal mupirocin ointment twice daily × 5 days
- 2% chlorhexidine showers daily × 5 days

Antibiotic prophylaxis controversial
- Should be considered for bites to hands, feet, face
- Wounds hard to clean—deep punctures, edema/crush injury
- Bites involving tendon, cartilage, or bone
- Bites in immunocompromised or asplenic host
- Bite prophylaxis antibiotics: amoxicillin-clavulanate
  - For penicillin-allergic patient, trimethoprim-sulfamethoxazole plus clindamycin
- Antibiotic treatment: oral unless infection rapidly spreads or patient is febrile or high risk; then IV

Bite organisms
- Most oral flora is polymicrobial in nature. Some bacteria are more specific to source of “bite.”
- Human bites: *Streptococcus viridans* common, *Eikenella corrodens*
  - “Fight bite” x-rays for cartilage divots, broken teeth, and formal identification
- Cat bites: *Pasteurella multocida*
  - 50% require surgery—puncture wounds to tendons/joints
- Dog bites: *P. multocida, P. canis*
- Marine injuries
  - *Mycobacterium marinum*
    - Slow culture at low temperature (30°C)
    - Noncaseating granulomas
    - Treatment: 3 months of minocycline or clarithromycin
  - *Erysipelothrix rhusiopathiae*
    - Erysipelas—fish handler’s (also swine handler’s) disease
    - Gram-positive bacillus
    - Painful, itchy, spreading, purple ring-shaped lesion
    - Treatment: oral penicillin
  - *Vibrio vulnificus*
    - Oyster bite
    - Bullae and necrotizing fasciitis from gram-negative motile rod
    - Gastroenteritis from eating bad oyster
    - Treatment: I&D and broad-spectrum antibiotics (ceftazidime)
  - Tick bite (Ixodes): Lyme disease
    - *Borrelia burgdorferi* (a spirochete)
    - Erythema migrans: bull’s-eye lesion
    - Vector: white-footed deer mouse in northeast and Pacific north
    - Knee effusions
  - Neurologic disease: Bell palsy common
    - Treatment: amoxicillin versus doxycycline
  - Rabies (neurotropic virus)
    - Raccoon/skunk/bat bites
    - CNS irritation, “hydrophobia,” paralysis, and death
    - Death if not treated before symptoms occur
    - Treatment: human rabies immune globulin
  - Septic bursitis
    - Similar pathology whether in olecranon, prepatellar, or pretribial bursa
    - Redness, swelling, pain, and subcutaneous fluctuance
    - About 80% caused by *S. aureus*, others streptococci
    - Chronic recurrent cases can be fungal or mycobacterial
- Aspiration with Gram stain and culture if redness is presence
- Treatment
  - Serial aspirations and oral antibiotics
  - IV antibiotics for systemic symptoms and in immunocompromised patients
  - Bursectomy for persistent or recurrent cases
- Tetanus
  - Potentially lethal neuroparalytic disease leading to trismus (lockjaw)
  - Exotoxin from anaerobe C. tetani
  - Tetanospasmin blocks inhibitory nerves.
- Deep wounds and devitalized tissues are at high risk.
  - Wounds more than 6 hours old, more than 1 cm deep, ischemic, crush, grade III
  - Contaminated with soil or feces, animal bite
- Vaccination
  - Tetanus toxoid (Td) 0.5-mL diphtheria-tetanus toxoid booster every 10 years
  - Adults with at-risk wounds, give Td booster
  - Status unknown or history of fewer than three doses: give both Td and tetanus immune globulin (TIG)

**Osteomyelitis**
- Exogenous: most common osteomyelitis in adults
- Acute osteomyelitis from open fracture or bone exposed at surgery
- Chronic osteomyelitis from neglected wounds: diabetic feet, decubitus ulcers
- Hematogenous: most common osteomyelitis in children
- Pediatric patients
  - Immature immune system
  - Metaphysis or epiphysis of long bones
  - Lower extremity more often than upper
- Adult patients
  - Immunocompromised (elderly, undergoing chemotherapy transplant recipient)
  - Vertebral most common adult hematogenous site
  - Patient undergoing dialysis—rib and spine osteomyelitis
  - IV drug abuser—medial or lateral clavicle osteomyelitis
- Acute osteomyelitis
  - Short duration, usually less than 2 weeks
  - Symptoms include tenderness, limb, refusal to use limb
  - Fever and systemic symptoms variable
- Laboratory findings:
  - CRP—most sensitive test (increased in ≈97%)
  - Most rapid rise and fall—good measure of treatment success
  - ESR—increased in approximately 90%
  - CBC—WBCs increased in only a third
  - Aspiration and biopsy cultures—most specific test
- Histopathology: bony spicules with live osteocytes surrounded by inflammatory cells
- Treatment
  - 6 weeks of antibiotics directed at specific organisms identified by culture

### Table 1.33 Bite Injuries

<table>
<thead>
<tr>
<th>SOURCE OF BITE</th>
<th>ORGANISM</th>
<th>PRIMARY ANTIMICROBIAL (OR DRUG) REGIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Streptococcus viridans (100%) Bacteroides spp. (82%) Staphylococcus epidermidis (53%) Corynebacterium spp. (41%) Staphylococcus aureus (29%) Peptostreptococcus spp. Eikenella spp.</td>
<td>Early treatment (not yet infected): amoxicillin/clavulanate (Augmentin) With signs of infection: ampicillin/sulbactam (Unasyn), cefoxitin, ticarcillin/clavulanate (Timentin), or piperacillin-tazobactam Patients with penicillin allergy: clindamycin plus either ciprofloxacin or trimethoprim/sulfamethoxazole Eikenella organisms are resistant to clindamycin, nafcillin/oxacillin, metronidazole, and possibly to first-generation cephalosporins and erythromycin; susceptible to fluoroquinolones and trimethoprim/sulfamethoxazole; treated with cefoxitin or ampicillin P. canis is resistant to doxycline, cephalexin, clindamycin, and erythromycin Antirabies treatment should be considered Only 5% of dog bite wounds become infected Amoxicillin/clavulanate, cefuroxime axetil, or doxycycline Cephalexin should not be used P. multocida is resistant to doxycline, cephalexin, and clindamycin; many strains are resistant to erythromycin Of cat bite wounds, 80% become infected; culture Amoxicillin/clavulanate or doxycycline Antirabies treatment is not indicated Amoxicillin/clavulanate, third-generation cephalosporin, ticarcillin/clavulanate (Timentin), ampicillin/sulbactam, or imipenem-clastatin Antirabies treatment is indicated Amoxicillin/clavulanate or doxycycline Antivenin therapy Ceftriaxone Tetanus prophylaxis</td>
</tr>
<tr>
<td>Dog</td>
<td>Pasteurella canis S. aureus Bacteroides spp. Fusobacterium spp. Capnocytophaga spp.</td>
<td>Amoxicillin/clavulanate (Augmentin) or clindamycin (adults); clindamycin plus trimethoprim/sulfamethoxazole; treated with cefoxitin or ampicillin</td>
</tr>
<tr>
<td>Cat</td>
<td>Pasteurella multocida S. aureus Possibly tularemia</td>
<td>Amoxicillin/clavulanate or doxycycline</td>
</tr>
<tr>
<td>Rat</td>
<td>Streptobacillus moniliformis Spirillum minus</td>
<td>Amoxicillin/clavulanate or doxycycline</td>
</tr>
<tr>
<td>Pig</td>
<td>Polymicrobial (aerobes and anaerobes)</td>
<td>Amoxicillin/clavulanate or doxycycline</td>
</tr>
<tr>
<td>Skunk, raccoon, bat</td>
<td>Varies</td>
<td>Amoxicillin/clavulanate or doxycycline</td>
</tr>
<tr>
<td>Pit viper (snake)</td>
<td>Pseudomonas spp. Enterobacteriaceae S. epidermidis Clostridium spp.</td>
<td>Antivenin therapy Ceftriaxone Tetanus prophylaxis</td>
</tr>
<tr>
<td>Brown recluse spider Catfish sting</td>
<td>Toxin Toxins (may become secondarily infected)</td>
<td>Dapsone Amoxicillin/clavulanate prophylaxis</td>
</tr>
</tbody>
</table>

Surgery is reserved for draining abscesses or failure to improve on antibiotics.

Subacute osteomyelitis: Brodie abscess
- Residual of acute osteomyelitis versus hematogenous seeding of growth plate trauma
- Painful limp with no systemic signs
- Adolescent to early adult (<25 years)—stronger immune system
- Localized radiolucency with sclerotic rim at metaphysis of long bones
- Almost exclusively *S. aureus* (may be lower virulence)
- Treatment: surgical débridement and 6 weeks of IV antibiotics
- Rule out tumors (chondroblastoma): "Biopsy all infections, culture all tumors."

Chronic osteomyelitis
- History
  - Prior trauma/surgery or soft tissue wound
  - Previous acute osteomyelitis or septic arthritis
  - Should be considered in all nonunions
  - Often chronic wound or draining sinus
- Laboratory findings
  - Less helpful, can be normal
  - Open bone biopsy/culture best test (sinus tract cultures not helpful)
- Histopathology
  - Dead bone (avascular) (osteocytes have no nuclei)
  - Fibrosis of marrow space
  - Chronic inflammatory cells
- Treatment
  - Surgery required for chronic osteomyelitis
  - Basic principles
    - Multiple procedures frequently required
    - Removal of infected hardware
    - Removal of dead bone, which serves as a "foreign object"
    - Débridement of bone until punctate bleeding is restored ("paprika sign")
    - Débridement of compromised or necrotic soft tissue
    - Consideration of preoperative sinus tract injection with methylene blue
    - Consideration of antibiotic spacers: PMMA cement versus biologics
    - Restoration of vascularity or soft tissue muscle coverage
    - Six weeks of antibiotics directed at specific cultures
    - Adequate minimal inhibitory concentration (MIC) of antibiotics at site of infection
- Host classification (Cierny-Mader; Table 1.34)
  - A: healthy
  - B: wound healing comorbidities
  - BL (local): compromised vascularity
  - BS (systemic): compromised immune system
  - Diabetes mellitus, malnutrition, end-stage renal disease, malignancy, alcoholism, rheumatologic diseases, immunocompromised status
  - HIV, immunosuppressive therapy, DMARDs
  - BL/S (combined local and systemic)
  - C: compromised patient (palliative care or amputation)
    - No quality-of-life improvement if cured
    - Morbidity of procedure exceeds that of the disease.
    - Poor prognosis, poor cooperation with care
- Anatomic lesion classification (Fig. 1.50)
  - I: medullary—nidus endosteal
    - Residual hematogenous or intramuscular infected nonunion
    - Treatment: unroofing
  - II: superficial—infection on surface defect of coverage
    - Full-thickness soft tissue wounds: venous stasis/pressure ulcer
    - Treatment: decortication and soft tissue coverage
  - III: localized—cortical infection without loss of stability
    - Infected fracture union with butterfly fragment or prior plate
    - Treatment: sequestrectomy, soft tissue coverage, with or without bone graft
  - IV: diffuse—permeative throughout bone, unstable before or after débridement
    - Periprosthetic infection, septic arthritis or infected nonunions
    - Treatment: stabilization, soft tissue coverage, and bone graft
- Imaging of osteomyelitis
  - Radiographs
  - Acute osteomyelitis
    - Soft tissue swelling (early)
  - Arterial disease, venous stasis, irradiation, straining, smoking
  - BS (systemic): compromised immune system
  - Diabetes mellitus, malnutrition, end-stage renal disease, malignancy, alcoholism, rheumatologic diseases, immunocompromised status
  - HIV, immunosuppressive therapy, DMARDs
  - BL/S (combined local and systemic)
  - C: compromised patient (palliative care or amputation)
    - No quality-of-life improvement if cured
    - Morbidity of procedure exceeds that of the disease.
    - Poor prognosis, poor cooperation with care

### Table 1.34 Chronic Osteomyelitis: Infected Host Types

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DESCRIPTION</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Normal immune response; nonsmoker</td>
<td>Minimal</td>
</tr>
<tr>
<td>B</td>
<td>Local or mild systemic deficiency; smoker</td>
<td>Moderate</td>
</tr>
<tr>
<td>C</td>
<td>Major nutritional or systemic disorder</td>
<td>High</td>
</tr>
</tbody>
</table>

![Medullary](image1.png)

![Superficial](image2.png)

![Localized](image3.png)

![Diffuse](image4.png)

*FIG. 1.50* Cierny’s anatomic classification of adult chronic osteomyelitis.
• Bone demineralization or regional osteopenia (≈2 weeks after infection)
• Chronic osteomyelitis
• Periosteal reaction, cortical erosions, bony lucency, and sclerotic changes
• Bony lysis around hardware and prosthetic joints
• **Sequestra**—dead bone nidus with surrounding granulation tissue
• **Involucrum**—periosteal new bone forming later
• **MRI best method to show early osteomyelitis and anatomic location**
  • Penumbra sign
  • Bright signal in surrounding bone
  • Darker abscess and sclerotic bone
  • Negative finding rules out osteomyelitis
  • Positive finding may overestimate extent of disease
• Fluorodeoxyglucose positron emission tomography (FDG-PET)
  • Shows malignancies and infections: increased glycolysis
  • Most sensitive test for chronic osteomyelitis
  • More specific than MRI or bone scan
• **Empiric treatment for osteomyelitis prior to definitive culture findings**
  • Newborn (up to 4 months of age)
    • *S. aureus*, gram-negative bacilli, and group B streptococci
    • Nafcillin or oxacillin plus a third-generation cephalosporin
    • If MRSA: vancomycin plus a third-generation cephalosporin
  • Children 4 months of age or older
    • *S. aureus* and group A streptococci
    • Nafcillin or oxacillin versus vancomycin (MRSA)
    • Immunization has almost eliminated *Haemophilus influenzae* bone infections.
  • Adults (21 years of age or older)
    • *S. aureus*
    • Nafcillin or oxacillin versus vancomycin (MRSA)
• **Antibiotic spacers/beads**
  • Provide very high antibiotic levels at local area
  • 2–4 g per bag (40 g) of cement (>2 g reduces compressive strength)
  • Pouch can be formed and covered with adherent film.
  • Antibiotics must be heat stable.
  • Cephalosporins, aminoglycosides, vancomycin, clindamycin
  • Antibiotics inactivated by heat must be avoided
  • Tetracycline, fluoroquinolones, polymyxin B, chloramphenicol
  • Antibiotics elute out over 2–6 weeks.
    • Elution increased with
      • Surface area—beads
      • Higher porosity—vacuum mixing should not be used.
      • Larger antibiotic crystals—cement should be mixed until doughy, then antibiotics added.
• **Atypical or unusual organisms**
  • *Salmonella osteomyelitis*—sickle cell
  • Microinfarcts of bone and bowel
  • Spleen dysfunction
  • Bone crisis versus diaphyseal osteomyelitis
  • *Pseudomonas* osteomyelitis
  • IV drug abuse and osteomyelitis of medial/lateral clavicle
• **Puncture wounds through rubber/synthetic shoes**
• **TB osteomyelitis**
  • One-third of the world is infected with TB.
  • One-third of TB in pediatric and HIV-positive patients is extrapulmonary.
  • Spine most common: Pott disease (spinal gibbus)
  • One-fourth of extrapulmonary TB is in hips and knees.
  • Often involves bones on both side of joint
• **Fungal osteomyelitis**
  • Long-term IV medications or parental nutrition
  • Immunosuppression by disease or drugs (RA, transplantation)
  • *Candida*—most common; is part of normal flora
  • *Aspergillus*—rare in bone
  • Regional varieties—via inhalation or direct inoculation
    • *Coccidioides*—southwest United States to South America
    • *Histoplasma*—soil and bird/bat guano, Ohio and Mississippi river valleys
    • *Blastomyces*—rotting wood, central southeastern United States
    • *Cryptococcus*—pigeon droppings, northwest United States/Canada
• **Treatment**
  • Débridement of osteonecrosis, resection of sinuses and/or synovitis
  • Antifungals: amphotericin
• **Chronic regional multifocal osteomyelitis (CRMO)**
  • (also chronic nonbacterial osteomyelitis [CNO])
  • Children/adolescents with multifocal bone pain but no systemic symptoms
  • Exacerbations and remissions, more than 6 months of pain
  • Autoinflammatory disease; a diagnosis of exclusion
  • No abscess, fistula, or sequestrum
  • Laboratory findings: WBC count normal; ESR, CRP may be elevated
  • X-rays demonstrate multiple metaphyseal lytic or sclerotic lesions.
  • Whole-body spin tau inversion recovery (STIR) MRI more sensitive
  • Culture results negative—antibiotics do not help
  • **Histologic findings**
    • Early: PMNs and osteoclasts
    • Later: lymphocytes, fibrosis, and reactive bone
      • Especially in the medial clavicle, distal tibia, and distal femur
  • Treatment: symptomatic; resolves spontaneously; NSAIDs help
• **SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome**
  • Also called acquired hyperostosis syndrome
  • Young to middle-aged adults with bone pain and skin involvement
  • Suspicion that *Propionibacterium acnes* serves as antigenic trigger
  • Humoral induction of sclerosis and erosions
  • Sternoclavicular region most commonly involved
  • Axial skeleton involvement and unilateral sacroiliitis common
  • Palmopustular psoriasis, acne, or hidradenitis suppurativa
  • Laboratory findings: ESR, CRP moderately elevated
  • Bone scan (gold standard): bull’s head sign, sacroiliac joint uptake
Septic arthritis

- Sources
  - Hematogenous spread
  - Extension of metaphyseal osteomyelitis at intraarticular physis
    - Proximal femur—most common
    - Proximal humerus, radial neck, distal fibula
  - Direct inoculation—penetrating trauma, iatrogenic complication

- Diagnosis
  - Progressive development of joint pain, swelling (effusion), warmth, redness
  - Progressive loss of function
  - Loading or moving a joint hurts
  - Differential diagnosis of acute monoarthritis
  - Gout/pseudogout—may be history of prior episodes
  - Reactive arthritis—uveitis, urethritis, heel/back pain, colitis, psoriasis
  - Viral arthritis
  - Fever and systemic symptoms more common in younger patients

- Laboratory findings
  - Elevations of CRP, ESR, WBC
  - Aspiration—best test
    - Cell count: greater than 50,000 WBCs/μL; left shift
    - Gram stain—helpful if positive
    - Cultures: aerobic and anaerobic
    - Crystals

- S. aureus most common bacteria, but following organisms should also be considered:
  - Group B streptococci (GBS): neonate
  - H. influenza: Unvaccinated children younger than 2 years
  - Kingella kingae: slower progressing or less virulent septic arthritis in young children
  - Toddler (aged 1–4 yr) with painful joint
  - After upper respiratory infection in fall/winter
  - Gram-negative coccobacilli—hard to culture; blood bottles should be used

- PCR should be considered

- Group A strep: post-varicella
- Neisseria gonorrhoeae: sexually active young adults
- P. acnes
  - Most common cause after mini–open repair of rotator cuff
  - Shoulder replacement (second only to S. aureus)
  - Indolent low-grade common contaminant
  - More than one culture needed; grows very slowly (7–10 days)
  - Gram-positive anaerobic rod that fluoresces under ultraviolet light
  - Less sensitive to cefazolin (penicillin, vancomycin, clindamycin)

- Fungal infections
  - Chronic effusions, synovitis
  - Immunocompromise: especially cellular immunity
  - IV drug abuse
  - Aspiration: 10,000–40,000 WBCs/μL, 70% PMNs

- Diagnosis: potassium hydroxide (KOH) versus 6-week culture

- Treatment
  - I&J
  - IV antibiotics best based on culture results
  - Empiric antibiotics based on Gram stain results:
    - Gram-positive cocci: vancomycin
    - Gram-negative cocci: ceftriaxone
    - Gram-negative rods: cefazidime, carbapenem, or fluoroquinolone
    - Negative Gram stain: vancomycin and cefazidime or fluoroquinolone
  - Progress can be monitored with CBC, ESR, CRP (best measure of success)

- Periprosthetic septic arthritis: see Chapter 5, Adult Reconstruction, for details.

Infectious risks of practice

- HIV infection
  - Obligate intracellular retrovirus
  - Primarily affects lymphocyte and macrophage cell lines
  - Decreases helper cells (CD4+ cells)
  - Approximately 50,000 new cases/year reported by the CDC
  - Increased in: homosexual men, patients with hemophilia, and IV drug abusers
  - One-fifth of those infected know they are HIV positive.
  - AIDS
    - Diagnosis requires an positive HIV test result plus one of the following:
      - One of the opportunistic infections (e.g., pneumocystis)
      - CD4+ cell count of less than 200 cell/μL (normal, 700–1200 cells/μL)

- Transmission rate
  - Increases with amount of blood exposed and viral load
  - Decreases with postexposure antiviral prophylaxis
  - From a contaminated needlestick: 0.3%
  - From mucous membrane exposure: 0.09%
  - From a blood transfusion: approximately 1 per 500,000 per unit transfused

- From frozen bone allograft: less than 1 per 1 million
  - Donor screening—most important factor in preventing viral transmission
  - No cases from fresh frozen bone allograft have been reported since 2001.
  - Most sensitive screen—nucleic acid amplification testing (NAAT)

- HIV positivity is not a contraindication to performing required surgical procedures.
  - HIV-positive patients more likely to have THA
  - Higher association with liver disease, drug abuse, coagulopathy
  - Development of acute renal failure and postoperative infection more likely
  - Asymptomatic HIV-positive individuals have no significant difference in short-term infection risks.

- Orthopaedic manifestations more common in later stages
  - Increased infections:
    - Polymyositis: viral muscle infection
    - Pyomyositis: S. aureus
    - TB
    - Bacillary angiomatosis (Bartonella henselae) from cats
    - Reactive arthritis (Reiter syndrome)
    - Non-Hodgkin lymphoma and Kaposi sarcoma
    - Osteonecrosis
Hepatitis
- Hepatitis B (HB)
  - Blood transmission: bite/sexual/occupational
  - Single-stick transmission rate in the unvaccinated: approximately 30%
  - Causes cirrhosis, liver failure, and hepatocellular carcinoma
  - Screening and vaccination have reduced the risk of transmission for health care workers.
  - Immune globulin is administered after exposure in unvaccinated persons.
  - Allografts are screened for HB surface antigen and HB core antibody.
- Hepatitis C (non-A, non-B) (HCV)
  - Blood transmission: two-thirds of U.S. HCV-positive individuals have IV drug abuse history; 2% of cases are occupational
  - Single-stick transmission rate ≈3%
  - Advances in screening have decreased the risk of transfusion-associated infection.
  - Most sensitive method to screen and test early:
    - PCR = NAAT
- Antibiotics
  - Prophylactic treatment of open fractures
    - Gustilo I and II fractures: first-generation cephalosporins the treatment of choice
    - Gustilo IIIA: first-generation cephalosporin plus an aminoglycoside
    - Gustilo IIIB (grossly contaminated): first-generation cephalosporin plus an aminoglycoside plus penicillin
  - Mechanisms of action of antibiotics are summarized in Table 1.35.
  - Antibiotic indications and side effects are listed in Table 1.36.
THROMBOPROPHYLAXIS

- Thromboembolic disease
  - Common orthopaedic complication
    - Thrombosis: clotting at improper site
    - Embolism: clot that migrates
  - Most clinically silent but can be fatal
  - Complications of thromboembolic disease:
    - Postthrombotic syndrome: chronic venous insufficiency
    - Venous hypertension (HTN)
    - Chronic skin issue with swelling, pain
    - Pigmentation, induration, ulceration
    - Recurrent deep venous thrombosis (DVT): risk four to eight times higher after first DVT
  - Pulmonary embolism (PE)
- Pathophysiology (Virchow triad) (Fig. 1.51)
  - Endothelial damage: trauma or surgery
    - Exposes collagen—triggers platelets
    - Platelets—three roles:
      - Adhesion and activation
      - Secretion of prothrombotic mediators
      - Aggregation of many platelets
    - Stasis: allows bonds of clotting proteins and cells
    - Immobility: pain, stroke, paralysis
    - Blood viscosity: polycythemia, cancer, estrogen
    - Decreased inflow: tourniquet, vascular disease
    - Decreased outflow: venous scarring, CHF

- Hypercoagulability
  - Clotting cascade’s final product is thrombin
  - Converts soluble fibrinogen to insoluble fibrin

Risk factors and epidemiology
- Reported risks of thromboembolic disease vary by:
  - Definitions: asymptomatic versus symptomatic
  - Location
    - Distal: those below popliteal space have very low PE risk
    - Proximal: those above popliteal space have higher PE risk
  - Patient-specific risks factors (Fig. 1.52)
    - Prior thromboembolic disease a strong risk factor
    - Risk increases exponentially with age (>40 years)
      (Fig. 1.53)
  - Genetic factors—thrombophilias
    - Decreased anticlotting factors
      - Antithrombin III, protein C, protein S deficiencies
      - Increased clotting factors or factor activity
        - Factor V Leiden
          - Mutated factor V not inactivated as effectively by activated protein C, so clotting process remains active for longer than normal
        - Elevated factor VIII
        - Hyperhomocysteinemia
        - Prothrombin G20210A (factor II mutation)

**FIG. 1.51** Left, Electronmicrograph panel (A through E). (A) Scanning electron micrograph (SEM) of free platelets. (B) SEM of platelet adhesion. (C) SEM of platelet activation. (D) Transmission electron micrograph of aggregating platelets. 1, Platelet before secretion; 2 and 3, platelets secreting contents of granules; 4, collagen of endothelium. (E) SEM of fibrin mesh encasing colorized red blood cells. Right, Illustration panel (A through H) showing venous thromboembolus formation. (A) Stasis. (B) Fibrin formation. (C) Clot retraction. (D) Propagation. (E–H) Continuation of this process until the vessel is effectively occluded. (From Miller MD, Thompson SR, editors: DeLee and Drez’s orthopaedic sports medicine: principles and practice, ed 4, Philadelphia, 2014, Saunders; platelet electron micrographs courtesy James G. White, MD, Department of Laboratory Medicine and Pathology, University of Minnesota School of Medicine; Miller MD et al: Review of orthopaedics, ed 6, Philadelphia, 2012, Saunders; and Simon SR, editor: Orthopaedic basic science, Rosemont, IL, 1994, American Academy of Orthopaedic Surgeons, p 492.)
Most common hypercoagulable genetic (primary) disorders

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Prevalence (%)</th>
<th>Venous thromboembolism patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.02</td>
<td>2</td>
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<tr>
<td>6.5</td>
<td>0.3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0.003</td>
<td>2</td>
</tr>
</tbody>
</table>

Decreased antithrombotic factors

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Increased prothrombotic factors

- Factor V Leiden–homozygous (C resistance)
- Factor V Leiden–heterozygous (C resistance)
- Elevated factor VIII
- Hyperhomocysteinemia
- Prothrombin G20210A (increased factor II)

The secondary hypercoagulable states

- Abnormalities of blood flow: Hyperviscosity, Venous stasis, Obesity, Postoperative state, Trauma
- Abnormalities of blood composition: Pregnancy, Paroxysmal nocturnal hemoglobinuria, Hyperlipidemia, Heparin-associated thrombosis
- Abnormalities of vessel wall: Oral contraceptives, Nephrotic syndrome, Paroxysmal nocturnal hemoglobinuria, Thrombotic thrombocytopenic purpura, Antiphospholipid syndrome, Vasculitis


- Procedure-specific factors (Fig. 1.54)
  - PE risk lower with distal procedures versus hip procedures
  - Risk higher with longer procedures
  - Total knee arthroplasty (TKA) has higher total DVT risk but lower PE risk
  - Risk with hip fracture is higher than that with THA.

- Diagnosis
  - Clinical diagnosis favors assessment of risk factors.
  - Physical exam is unreliable: most cases are asymptomatic.
  - DVTs can cause calf pain, palpable cords, swelling.
  - 50% with classic signs have no DVT according to studies
### Table 1.54

<table>
<thead>
<tr>
<th>Procedure</th>
<th>sDVT (%)</th>
<th>PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hospital admission</td>
<td>0.048–0.07</td>
<td>0.023–0.03</td>
</tr>
<tr>
<td>Major orthopaedic procedures: THA, TKA, HFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In 2 weeks no prophylaxis</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>In 35 days no prophylaxis</td>
<td>2.8</td>
<td>1.5</td>
</tr>
<tr>
<td>In hospital with prophylaxis</td>
<td>0.26–0.8</td>
<td>0.14–0.35</td>
</tr>
<tr>
<td>In 35 days with prophylaxis</td>
<td>0.45</td>
<td>0.20</td>
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<tr>
<td>Knee arthroscopy</td>
<td>0.25–9.9</td>
<td>0.028–0.17</td>
</tr>
<tr>
<td>ACL reconstruction</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Hip arthroscopy</td>
<td>0–3.7</td>
<td>0</td>
</tr>
<tr>
<td>Shoulder arthroscopy</td>
<td>0.01–0.26</td>
<td>0.01–0.21</td>
</tr>
<tr>
<td>Shoulder fracture</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Shoulder arthroplasty</td>
<td>0.19–0.2</td>
<td>0.1–0.4</td>
</tr>
<tr>
<td>Elbow arthroplasty</td>
<td>—</td>
<td>0.25</td>
</tr>
<tr>
<td>Foot and ankle surgery</td>
<td>0–0.22</td>
<td>0.02–0.15</td>
</tr>
<tr>
<td>Ankle fracture</td>
<td>0.05–2.5</td>
<td>0.17–0.47</td>
</tr>
<tr>
<td>Ankle arthroscopy</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

*ACL, Anterior cruciate ligament; HFS, hip fracture surgery; PE, pulmonary embolism; sDVT, symptomatic deep vein thrombosis; THA, total hip arthroplasty; TKA, total knee arthroplasty.*


- 50% with venogram positive for clot have normal physical findings
- PEs: most asymptomatic
  - Signs/symptoms include pleuritic chest pain, dyspnea, tachypnea
  - Saddle emboli can manifest as death.
- Laboratory studies
  - D-dimer studies not helpful after injury/surgery but negative result rules out significant clot.
- ECG: rule out MI
  - Nonspecific findings; most common finding is sinus tachycardia.
- Radiologic studies (Fig. 1.55)
  - Venogram—best for distal (below popliteal) lesions (clinical relevance?)
  - Duplex compression ultrasound—most practical
    - Noninvasive, easily repeatable bedside test
    - Finding of “noncompressible vein” about 95% sensitive/specific
    - Guidelines strongly against routine duplex screening
  - Chest x-ray
    - Early findings: usually normal, “oligemia,” or prominent hilum (Fig. 1.56B)
    - Late findings: wedge or platelike atelectasis (see Fig. 1.56C)
  - Spiral CT angiography—best for suspected PE
  - Ventilation-perfusion (V/Q) scan—most helpful for dye-sensitive patients

**Thromboembolic prophylaxis**
- Preventing DVTs has been shown to be possible, although whether such prevention avoids death is unproven.
- Guidelines vary in their recommendations (Fig. 1.57).
- Prophylaxis recommended for all patients undergoing arthroplasty.
  - Those undergoing THA may benefit from extended treatment (≈30 days).
- For patients without risk-related conditions, prophylaxis is not recommended for
  - Upper extremity procedures, arthroscopic procedures, surgery for isolated fractures at knee and below
- Mechanical measures
  - Early mobilization
  - Graduated elastic hose—not sufficient alone
  - Intermittent pneumatic compression devices (IPCDs)
    - Stimulate fibrinolytic system
    - Low bleeding risks
    - Grade IC by 2012 American College of Chest Physicians (ACCP) guidelines
  - Continuous passive motion (CPM) of no benefit
- Pharmacologic prophylaxis:
  - Surgical Care Improvement Project (SCIP) quality measures require DVT prophylaxis.
- **Aspirin**
  - Irreversibly binds and inactivates COX in platelets, thereby reducing thromboxane A₂
  - Weakest: Use of IPCD encouraged
FIG. 1.55 Top left to right, Venogram showing deep vein thrombosis. Intraluminal filling defects (arrows) seen on two or more views of a venogram. The left and middle images are at the knee, and the right image is at the hip. Middle, Doppler ultrasound for proximal DVT in femoral vein thrombosis. (A) Longitudinal view shows presence of flow (light blue) in the more superficial vein over an occlusive thrombus (dark gray). (B) A transverse view without compression shows an open superficial vein, appearing as a black oval (white arrow) and a thrombosed deeper vein as a dark gray circle with an echogenic center (red arrow). (C) A transverse view with compression shows the flattened compressible superficial vein (white arrow) and the unchanged noncompressible thrombosed deeper vein (red arrow). Bottom left, Spiral CT pulmonary angiography. (A) Large pulmonary embolism (arrows). (B) Normal CT. Right images, high probability V/Q scan showing full lung fields on ventilation scan (upper) and multiple areas lacking tracer on the perfusion scan (lower); ant, Anterior; LAO, left anterior oblique; post, posterior; RPO, right posterior oblique. (V/Q panel from Jackson JE, Hemingway AP: Principles, techniques and complications of angiography. In Grainger RG, editor: Grainger & Allison’s diagnostic radiology: a textbook of medical imaging, ed 4, Philadelphia, 2011, Churchill Livingstone. Original images courtesy Austin Radiological Association and Seton Family of Hospitals.)
FIG. 1.56 Chest radiographs. (A) Diffuse bilateral fluffy patchy infiltrates, worse at bases, are consistent with ARDS (acute respiratory distress syndrome). (B) A focal area of oligemia in the right middle zone (Westermark sign [white arrow]) and cutoff of the pulmonary artery in the upper lobe of the right lung are both seen with acute pulmonary embolism. (C) The peripheral wedge-shaped density without air bronchograms at lateral right lung base (Hampton hump [black arrow]) develops over time after a pulmonary embolism. (B from Krishnan AS, Barrett T: Images in clinical medicine: Westermark sign in pulmonary embolism, N Engl J Med 366:e16, 2012; C from Patel UB et al: Radiographic features of pulmonary embolism: Hampton hump, Postgrad Med J 90:420–421, 2014.)

Recommendations on prevention of VTE in hip and knee arthroplasty

<table>
<thead>
<tr>
<th>Strong + Moderate – Weak * Consensus ? Inconclusive</th>
<th>Notes from other guidelines:</th>
<th>1 ACCP, 2 NICE, 3 AHRO</th>
</tr>
</thead>
<tbody>
<tr>
<td>! No “screening” duplex US</td>
<td>DRUGS: LMWH, fondaparinux, dabigatran, rivaroxaban, VKA, aspirin1</td>
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</tr>
<tr>
<td>+ History of normal risks of VTE and bleeding, use drugs and/or IPC</td>
<td>Discuss with medical team, stop 1 week prior2</td>
<td></td>
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<tr>
<td>+ D/C platelet inhibitors preop (aspirin, clopidogrel, prasugrel)</td>
<td>Cautions with drugs and neuraxial1; wait 12 hours after drugs2</td>
<td></td>
</tr>
<tr>
<td>+ Neuraxial anesthesia to decrease bleeding (no effect on VTE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ask history of previous VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Hx of VTE, get IPC and drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Ask Hx of bleeding disorder (hemophilia) and active liver disease</td>
<td></td>
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<tr>
<td>* Hx of bleeding disorder (hemophilia or active liver disease) only IPC</td>
<td>If bleeding risk, IPC or nothing1; if bleeding risk &gt; clotting risk, IPC2</td>
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<tr>
<td>* Discuss duration with patient</td>
<td>≥10 days, consider 35 days1</td>
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</tr>
<tr>
<td>* Early mobilization</td>
<td></td>
<td></td>
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<tr>
<td>? Assess other clotting risk factors</td>
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<td></td>
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<tr>
<td>? Assess other bleeding risk factors</td>
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<td>? No one technique optimal</td>
<td>Drugs and IPC1,2; D/C drugs when TKA mobile2</td>
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<tr>
<td>? IVC filter</td>
<td>If VTE risks high and contraindication to prophylaxis2</td>
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Guideline title | Source: |
<table>
<thead>
<tr>
<th></th>
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<tr>
<td>2011 AAOS Preventing Venous Thromboembolic Disease</td>
<td><a href="http://www.aaos.org/research/guidelines">http://www.aaos.org/research/guidelines</a></td>
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<td>2012 ACCP Prevention of VTE in Orthopedic Surgery Patient</td>
<td><a href="http://journals.publications.chest.net/">http://journals.publications.chest.net/</a></td>
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<tr>
<td>2012 AHRQVTE Prophylaxis in Orthopedic Surgery, CER 49</td>
<td><a href="http://effectivehealthcare.ahrq.gov/">http://effectivehealthcare.ahrq.gov/</a></td>
</tr>
</tbody>
</table>

FIG. 1.57 Recommendations on prevention of VTE in hip and knee arthroplasty. Hx, history; US, ultrasonography.

- Low bleeding risk: Should be considered for patients at higher risk for bleeding.
- Warfarin (Coumadin)
  - Prevents vitamin K γ-carboxylation in liver
  - Inhibits factors II, VII, IX, X, and proteins C and S
  - Vitamin K and fresh frozen plasma can reverse
  - Multiple reactions with drugs and diet
  - Must be monitored with international normalized ratio (INR; goal, 2–3)
- Heparin
  - Activates antithrombin III (ATIII), which then inactivates factor Xa and thrombin
  - Protamine sulfate can reverse
  - Short half-life: 2 hours
  - High bleeding rate in arthroplasty
  - Binds platelets—heparin-induced thrombocytopenia
  - Low-molecular-weight heparin (LMWH)
  - Reversibly inhibits factor Xa through ATIII and factor II
PERIOPERATIVE DISEASE AND COMORBIDITIES

Orthopaedic surgeons who evaluate their patients with care preoperatively can be rewarded with fewer perioperative problems.

Goals include finding correctable issues and identifying risks to provide accurate risk/benefit assessment for proper consent.

Cardiac issues

Coronary artery disease (CAD): leading cause in those older than 35 years

Leading cause of cardiac death in young sports population: hypertrophic cardiomyopathy

American College of Cardiology/American Heart Association (ACC/AHA) elements for assessing risk

Clinical risk factors in perioperative cardiac risk

Major predictors

- Unstable/severe angina, recent MI (<6 weeks)
- Worsening or new-onset CHF
- Arrhythmias
- Atrioventricular (AV) block
- Symptomatic ventricular dysrythmia: bradycardia (<30 beats/min), tachycardia (>100 beats/min)
- Severe aortic stenosis or symptomatic mitral stenosis

Other

- Prior ischemic heart disease
- Prior CHF
- Prior stroke/TIA
- Diabetes
- Renal insufficiency (creatinine >2 mg/dL)

Functional exercise capacity—measured in metabolic equivalents (METs)

- MET: 3.5 mL O₂ uptake/kg/min
- Perioperative risk elevated if unable to meet 4-MET demand
  - Walk up flight of steps or hill (= 4 METs)
  - Heavy work around house (>4 METs)
  - Can patient walk four blocks or climb two flights of stairs?

Surgery-specific risk:

- High risk (>5% risk of death/MI)
- Aortic, major or peripheral vascular procedures
- Intermediate risk (1%–5% risk of death/MI)
- Orthopaedic, ENT, abdominal/thoracic or procedures
- Low risk (<1% risk of death/MI)—usually do not need further clearance

Ambulatory surgery, endoscopic or superficial procedures

Twelve-lead ECG if:

- CAD and intermediate-risk procedure
- One clinical risk factor and intermediate-risk procedure
- Noninvasive evaluation of left ventricular function if:
  - Three or more clinical risk factors and intermediate-risk procedure
  - Dyspnea of unknown origin
  - CHF with worsening dyspnea without testing in 12 months

β-Blockers and statins should be continued around the time of surgery.

Acetylsalicylic acid (ASA) should be stopped 7 days prior to surgery.

Cardiology consultation should be considered for patients taking other agents (clopidogrel, prasugrel).

- Risk of stent thrombosis balanced with that of surgical bleed

Shock

Cardiovascular collapse with hypotension, followed by impaired tissue perfusion and cellular hypoxia. May be a result of orthopaedic pathology or a complication of surgery.

Metabolic consequence

- O₂ is unavailable—no oxidative phosphorylation
- Cells shift to anaerobic metabolism and glycolysis
- Pyruvate is converted to lactate—metabolic acidosis
- Lactate—indirect marker of tissue hypoperfusion

Best measures of adequate resuscitation

- Clinical measure of organ function: urine output more than 30 mL/h

- Other
• Laboratory measure: serum lactate less than 2.5 mg/dL.

■ Types of shock
  - Neurogenic shock
    • High spinal cord injury (also anesthetic accidents)
    • Loss of sympathetic tone and of vasomotor tone of peripheral arterial bed
    • Bradycardia, hypotension, warm extremities
    • Treatment: vasoconstrictors and volume
  - Septic shock (vasogenic)
    • Number one cause of ICU death
    • Mortality 50%
    • Bacterial toxins stimulate cytokine storm.
    • Examples: gram-negative lipopolysaccharides
    • Toxic shock superantigen
    • Inflammatory mediators cause endothelial dysfunction and peripheral vasodilation
    • Treatment
      • Identification and treatment of infections
      • Prompt resection of dead tissue
      • Appropriate antibiotics
  - Cardiogenic shock
    • Bad pump
      • Extensive MI, arrhythmias
    • Blocked pump (obstructive shock)
      • Massive “saddle” pulmonary embolism
    • Tension pneumothorax
      • Decreased lung sounds, hypertympany, tracheal deviation
      • Treated with needle decompression followed by tube thoracostomy
    • Cardiac tamponade
      • Beck triad: hypotension, muffled heart sounds, neck vein distension
      • Pulsus paradoxus
        • Decreased systolic BP with inspiration
      • Treatment: pericardiocentesis
  - Hypovolemic shock
    • Most common shock of trauma
    • Volume loss from bleeds or burns
      • “Third spacing” also a cause
    • Neuroendocrine response: save heart and brain
    • Peripheral vasoconstriction
      • BP may be normal
      • Pale, cold, clammy extremities
    • Percentage of blood loss key to symptoms/signs
      • Class I: up to 15% blood volume loss
        • Vital signs can be maintained.
        • Pulse below 100 beats/min
      • Class II: 15%–30% blood volume loss
        • Tachycardia (>100 beats/min), orthostatic
        • Anxious
        • Increased diastolic BP
      • Class III: 30%–40% blood volume loss
        • Decreased systolic BP
        • Oliguria
        • Confusion, mental status changes
      • Class IV: more than 40% blood volume loss
        • Life threatening; patient is obtunded
        • Narrowed pulse pressure
        • Immeasurable diastolic BP
    • Treatment
      • First, ABCs of resuscitation: then, bleeding must be stopped.
  - Blood products make better resuscitation fluids than saline.

■ Perioperative pulmonary issues
  - Higher in cases that involve thorax such as scoliosis
  - Highest in patients with prior disease
  - Spinal/epidural anesthesia favored over general
  - Medical treatment should be maximized around surgery.
  - COPD
    • Symptomatic COPD: anticholinergic inhalers (ipratropium)
    • May require corticosteroids
  - Asthma
    • Presence of wheezes or shortness of breath: β-agonist inhalers (albuterol)
    • Perioperative oral steroids safe
      • Systemic glucocorticoid should be considered if forced expiratory volume in 1 minute (FEV₁) or peak expiratory flow rate (PEFR) is below 80% predicted values/personal best.
  - Postoperative atelectasis
    • Like the associated cough, the workup is usually nonproductive.
    • Deep breathing/incentive spirometry—equally effective
  - Postoperative pneumonia takes up to 5 days to manifest.
    • Productive cough, fever/chills, increased WBC count
    • Radiograph: pulmonary infiltrates
  - Smoking cessation improves outcomes
    • Patients should stop 6–8 weeks preoperatively.
    • Nicotine supplements do no harm to wound.
    • Fewer pulmonary complications
      • Smokers have six times more pulmonary complications.
    • Fewer wound healing issues and wound infections
    • Lower nonunion rate
    • Shoulder, neck, and thoracic pain in smokers
      • Prompts careful evaluation of lung fields
      • Superior sulcus tumor (Pancoast tumor)
        • Intrinsic atrophy of hand—C8–T1
  - Acute respiratory distress syndrome (ARDS)
  - Pulmonary failure due to edema (see Fig. 1.56A)

■ Pathophysiology
  - Complement pathway activated
  - Increased pulmonary capillary permeability
  - Intravascular fluid floods alveoli
  - Results
    • Hypoxia, pulmonary HTN
    • Right heart failure
    • 50% mortality
  - Etiology
    • Blunt chest trauma, aspiration, pneumonia, sepsis
    • Shock, burns, smoke inhalation, near drowning
    • Orthopaedic: Long-bone trauma
  - Clinical symptoms
    • Tachypnea, dyspnea, hypoxia, decreased lung compliance
    • $\text{Pa}_O_2/\text{Fi}_O_2$ ratio below 200
  - Imaging
    • Radiographs: diffuse bilateral infiltrates, “snowstorm”
    • CT: ground glass appearance
  - Treatment
    • Prompt diagnosis and treatment of musculoskeletal infections
    • Prompt treatment of long-bone fractures
    • Ventilation with positive end-expiratory pressure (PEEP)
    • 100% $O_2$
Fat emboli syndrome—classic clinical triad

- Petechial rash: fat to skin
- Neurologic symptoms: fat to brain
  - Mental status changes: confusion, stupor
  - Rigidity, convulsions, coma
- Pulmonary collapse: fat showers lung
- ARDS: hypoxia, tachypnea, dyspnea
- Associated with long-bone fractures

Bleeding and blood products

- Bleeding complications can be avoided through preoperative identification of risk.
- Common inherited bleeding disorders
  - Von Willebrand disease: autosomal dominant
    - Most common genetic coagulation disorder
  - Von Willebrand factor dysfunction
    - Binds platelets to endothelium
    - Carrier for factor VIII
  - Treatment: desmopressin
- Hemophilia A (VIII): X-linked recessive
  - Hemophilia B (IX) Christmas disease: X-linked recessive

Medicines/supplements that should be stopped prior to surgery

- Platelet-inhibitor drugs (aspirin, clopidogrel, prasugrel, NSAIDs)
- Drugs that cause thrombocytopenia
  - Penicillin, quinine, heparin, LMWH
- Anticoagulants (see earlier discussion on DVT)
- Supplements
  - Fish oil, omega-3 fatty acids, vitamin E
  - Garlic, ginger, Ginkgo biloba
  - Dong quai, feverfew

Diseases associated with increased bleeding

- Chronic renal disease—uremia causes platelet dysfunction
- Chronic liver failure—decreased liver proteins of clotting cascade

Techniques to avoid blood loss at surgery

- Tourniquets: tissue effect relates to time and pressure
  - Used no longer than 2 hours
  - Time to restoration of equilibrium
    - 5 minutes after 90 minutes of use
    - 15 minutes after 3 hours
  - Prolonged use can cause tissue damage.
  - Nerve damage compressive (not ischemic)
  - Electromyography: subclinical abnormalities in 70% with routine use
  - Slight increase in pain
  - Wider tourniquets distribute forces
  - Pad underneath prevents skin blisters in TKA
  - Lowest pressure needed for effect should be used
    - 100–150 mm Hg above systolic BP
    - 200 mm Hg upper extremity
    - 250 mm Hg lower extremity
- Tranexamic acid
  - Synthetic lysine analogue; acts on fibrinolytic system
  - Competitive inhibitor of plasminogen activation
  - Reduces blood loss with no increase in DVT.
- Temperature
  - Mild hypothermia increases bleeding time and blood loss.
  - Intraoperative “cell saver” may be cost-effective if:
    - About 1000 mL of blood loss is expected
    - Recovery of 1 or more unit of blood is anticipated.
  - Techniques not yet found to be effective or cost-effective

- Bipolar sealant, topical sealsants, autologous donation
- Reinfusion systems, routine transfusions over 8 g/dL Hb

Preoperative techniques to address anemia

- Oral iron 30–45 days preoperatively
- Vitamin C increases iron absorption
- Folate and vitamin B12 deficiency also a source of anemia
- Erythropoietin if preoperative Hb below 13

Transfusions

- Ratio of 1:1:1 blood product resuscitation is superior to saline fluid
- Preoperative Hb most significant predictor of need
- Various guidelines for when to transfuse
  - Hb less than 6 g/dL: transfusion
  - Hb 7–8 g/dL: transfusion of postoperative patients
  - Hb 8–10 g/dL: transfusion of symptomatic patients
- Restrictive transfusion strategies
  - Lower 30-day mortality trend
  - Lower infection risk trend
  - Greatest benefits to orthopaedic patients
  - No difference in functional recovery

Transfusions risks

- Leading risk: transfusion of wrong blood to patient
  - Occurs in 1 in 10,000 to 1 in 20,000 RBC units transfused
- Transfusion reactions
  - Febrile nonhemolytic transfusion reaction
    - Most common
    - 1–6 hours post-transfusion
    - From leukocyte cytokines released from stored cells
    - Leukoreduction decreases incidence
  - Acute hemolytic transfusion reaction
    - Medical emergency
    - ABO incompatibility
      - IgM anti-A and anti-B, which fix complement
    - Rapid intravascular hemolysis
    - Classic triad: fever, flank pain, red/brown urine (rare)
      - Can cause disseminated intravascular coagulation (DIC), shock, and acute renal failure (ARF) due to acute tubular necrosis (ATN)
    - Positive direct antiglobulin (Coombs) test result
- Delayed hemolytic transfusion reactions
  - Reexposure to previous antigen (i.e., Rh or Kidd)
  - History of pregnancy, prior transfusion, transplantation
  - 3–30 days post-transfusion
  - Anemia, mild elevation of unconjugated bilirubin, spherocytosis
- Anaphylactic reactions: about 1 in 20,000
  - Rapid hypotension, angioedema
  - Shock, respiratory distress
  - Frequently involve anti-IgA and IgE antibodies
  - Treatment: cessation of transfusions, ABCs of resuscitation, epinephrine
  - Urticarial reactions: about 1%–3%
    - Mast cell/basophils release of histamine—hives
- Infectious risks
  - Bacterial: 0.2 per million packed red blood cell (PRBC) units transfused
  - Gram-positive organisms
  - Cryophilic organisms: Yersinia, Pseudomonas
  - HTLV—approximately 1 in 2 million
  - HIV—approximately 1 in 2 million
  - Hepatitis C—approximately 1 in 2 million

Chronic kidney disease (CKD)

- Most common organisms:
  - Gram-negative organisms
  - Acute interstitial nephritis (AIN): fever, eosinophils
  - Ischemia, sepsis, nephrotoxic drugs

Prerenal renal failure (most common ARF): decreased kidney perfusion

- Edema, HTN, urinary output less than 30 mL/hour

Postrenal ARF: obstruction

- History of pregnancy, prior transfusion, reexposure to previous antigen (i.e., Rh or Kidd)

Neurogenic atonic bladder

- Opioids, antidepressants, pseudoephedrine,
  “Neurogenic” atonic bladder
- Spinal trauma, tumor, stroke, diabetes

Excess fluid/long procedures

- Poor BP control
- Increased bleeding complications
- Increased cardiovascular risk
- Retained phosphate and secondary to albumin loss greater than 30 mg/day
- Acute interstitial nephritis (AIN): fever, eosinophils

Acute tubular necrosis (ATN)

- Hyperkalemia can be fatal.

Increased cardiovascular risk

- For blood potassium level more than 5.5 mmp/L, dialysis should be considered.
  - 100–150 mm Hg above systolic (IO) urinary catheter should be used.
  - 200 mm Hg upper extremity
  - 250 mm Hg lower extremity

ARF due to acute tubular necrosis (ATN)
Renal and urologic issues

ARF (acute kidney injury [AKI])
- Edema, HTN, urinary output less than 30 mL/hour (<0.5 mL/kg/h)
- Laboratory findings: creatinine increased over 1.5 times baseline
  - Hyperkalemia can be fatal.
    - For blood potassium level more than 5.5 mmp/L, dialysis should be considered.
- Prerenal renal failure (most common ARF): decreased kidney perfusion
- Hypovolemia/hypotension from blood loss
- Intrinsic renal failure
  - ATN: most frequent intrinsic ARF
  - Ischemia, sepsis, nephrotoxic drugs
  - Myoglobin from rhabdomyolysis
  - Acute interstitial nephritis (AIN): fever, eosinophils in blood/urine
- Glomerular disease: hematuria, proteinuria, HTN, edema
  - SLE, poststreptococcal, IgA nephropathy, hepatorenal
- Postrenal ARF: obstruction

Chronic kidney disease (CKD)
- Definition: GFR below 60 mL/min per 1.73 m² or urine albumin loss greater than 30 mg/day
  - Retained phosphate and secondary to hyperparathyroidism
  - Causes increased extraskeletal calcification
- High perioperative complications
  - Increased cardiovascular risk
  - Hyperkalemia and fluid adjustments
  - Increased bleeding complications
  - Poor BP control
  - Higher infection rates
  - Higher complications/revisions
  - Higher morbidity

Perioperative urinary retention
- Outflow obstructions: benign prostatic hypertrophy (BPH) in men (common)
- Bladder muscle (detrusor) compromise
- Overdistention
  - Excess fluid/long procedures
  - Neurogenic
    - Spinal trauma, tumor, stroke, diabetes
    - “Neurogenic” atomic bladder
  - Medications
    - Anticholinergic and sympathomimetic drugs
    - Opioids, antidepressants, pseudoephedrine, diphenhydramine
- Can cause postrenal ARF (AKI)
- Associated with higher rates of urinary tract infections
- Increased 2-year mortality after hip fracture
- Treatment
  - α-Blockers—tamsulosin 0.4 mg/day
  - Bladder ultrasound if no voiding by 3–4 hours
  - If ultrasound shows more than 400–600 mL, in-and-out (IO) urinary catheter should be used.
  - Trauma patient—no catheter if bloody meatus or scrotal hematoma present

Perioperative UTI
- “Irritative symptoms”: dysuria, urgency, frequency
- Account for 30%–40% of hospital-acquired infections
- Most common organisms: *Escherichia coli* and *Enterococcus*

Diagnosis
- If symptoms, urinalysis and culture/sensitivity testing
- WBCs (leukocyte esterase positive)
- Bacterial count over 10⁷ CFU/mL, treated preoperatively
- Treatment
  - Antibiotics for gram-negative organisms
    - Trimethoprim-sulfamethoxazole or fluoroquinolone

GI motility disorders (Fig. 1.58)

1.5% of hip/knee arthroplasties

Common presentation
- Abdominal pain
- Distention
- Nausea with or without vomiting

Prevention
- Chewing gum: vagal (parasympathetic stimulation)
- Early mobility
- Spinal (sympathetic block)
- Limiting dose and length of IV opioids

Postoperative adynamic ileus
- Gut autonomic nerve imbalance:
  - More common in spine (≥7%) and joint arthroplasty (≥1%)
- X-rays: dilated small and large bowel (see Fig. 1.58A)
- Treatment: nothing by mouth status, nasogastric tube
  - Electrolyte control
  - Cessation of narcotics

Superior mesenteric artery (SMA) syndrome (cast syndrome)
- Occlusion of duodenum by SMA
- Orthopaedic causes
  - Hip spica cast
  - Following scoliosis surgery
  - Following THA with severe hip flexion contracture
  - Following traumatic quadriplegia
- Also found in patients with rapid, large weight loss
- X-rays: distended stomach and upper duodenum (see Fig. 1.58B)
- CT
  - Aortomesenteric artery angle less than 25 degrees
  - Aortomesenteric distance less than 8 mm
- Treatment: nothing by mouth status, nasogastric tube

Acute colonic pseudoobstruction (Ogilvie syndrome)
- Large bowel dilation
- Abdominal distension the prominent symptom
- Colonic perforation should be avoided.
- Risk factors
  - Elderly or male patient
  - Previous bowel surgery
  - Diabetes, hypothyroidism
  - Electrolyte disorders
- Radiographic findings
  - Distended transverse and descending colon and cecum (see Fig. 1.58C)
  - Colonic diameter more than 10 cm risks perforation.
- Treatment
  - Nothing by mouth status
  - Neostigmine
  - Colonic decompression

Pseudomembranous colitis: potentially fatal diarrhea
- Most common antibiotic-associated colitis
- Change in colon flora favors *Clostridium difficile*
- Makes enterotoxin-A and cytotoxin-B
- Many antibiotics
  - Clindamycin, fluoroquinolones
Basic Sciences

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• Penicillins and cephalosporins
• Can become severe fulminant colitis
• Toxic megacolon and perforations
• Risk factors
  • Elderly hospitalized patient
  • Severe illness
  • Antibiotic use
  • Proton pump inhibitor use
• Diagnosis
  • Watery diarrhea with fever
  • Leukocytosis, lower abdominal pain
• Laboratory findings
  • WBC count more than 15,000 cells/μL
  • Stool specimen should be tested for *C. difficile* toxin
  • PCR or ELISA
  • KUB (kidney, ureter, bladder) (plain abdominal) radiograph
  • Toxic megacolon: greater than 7 cm
  • Thumbprinting (see Fig. 1.58D)

### Perioperative hepatic issues

• Liver failure: critical for producing proteins and metabolizing toxins
• Laboratory findings
  • Increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin
  • INR above 1.5, low platelets (<150,000 cells/μL)
• Acute—most commonly viral and drug induced
  • Acetaminophen—number one cause in United States
  • Other toxins: alcohol, occupational, mushrooms
  • Viral hepatitis
• Chronic—cirrhosis is end-stage fibrosis of liver
  • Common: hepatitis (B, C), alcoholism, hemochromatosis
• Classifications can be helpful to estimate risks
  • Child classification—most widely used
  • Based on laboratory results and physical examination

• Model for End-Stage Liver Disease (MELD) score
  (http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model)
  • Formula based on bilirubin, INR, creatinine
  • Studies highlight mortality at 90 days relative to MELD score
    • <9: about 2% mortality
    • 10–19: about 6% mortality
    • 20–29: about 20% mortality
    • 30–39: about 53% mortality
    • >40: about 71% mortality
  • Complication rates from surgery are extremely high.
  • In patients undergoing arthroplasty, MELD score above 10 predicted
    • Three times the complication rate
    • Four times the rate death

### Perioperative CNS issues

• Stroke
  • Rare (0.2% of joint arthroplasties)
  • Mortality roughly 25% at 1 year
  • Ischemic more common than hemorrhagic
• Risk factors
  • Advanced age, CVA, TIA
  • MI, coronary artery bypass graft, atrial fibrillation, or ECG rhythm abnormality
  • Left ventricular dysfunction
  • Cardiac valvular disease
  • General anesthesia higher risk than regional
• Diagnosis: head CT or MRI
• Treatment: ABCs of resuscitation, hospitalist/neurology consultation

• Delirium: approximately 40% in patients with hip fractures
  • Fluctuating levels of consciousness
  • Impairment of memory and attention
  • Disorientation, hallucinations, agitation
  • Associated with increased length of stay
  • Decubitus ulcers, failure to regain function
  • Feeding issues, urinary incontinence
  • Mortality and nursing home placement
• Risk factors
  • Older patients
  • History of prior postoperative confusion
  • History of alcohol abuse
  • Acute surgery more than elective

• Night-time surgery  
• Long duration of anesthesia  
• Intraoperative pressures below 80 mm Hg  
• Use of meperidine (Demerol)  
• Diagnosis: anemia ruled out, infection, electrolyte issues  
• Treatment  
  • O₂ saturation above 95%, systolic BP above 90 mm Hg  
  • Correction of medical issues  
  • Family/friends  
  • Medications for sedation: used with caution  
  • Restraints as last resort

### Special anesthesia issues

- Obstructive sleep apnea (OSA)
  - Increased radiation exposure associated with
    - Should be considered for every fluoroscopic case
    - Imaging of larger body parts
    - Positioning the extremity closer to the x-source
  - Increased MI, arrhythmias (atrial fibrillation)
  - Increased risks for aspiration/intubation
  - Increased postoperative O₂ desaturation
  - Increased intubation, aspiration pneumonia, ARDS
  - Increased MI, arrhythmias (atrial fibrillation)
  - Screening tools: STOP-BANG (Fig. 1.59)
    - Snoring, tired, observed apnea, pressure (HTN) BMI over 35, age older than 50 years, neck circumference larger than 40 cm, gender male
    - Five or more factors present—high risk of severe OSA
  - Best practices
    - Initiation or continuation of CPAP use
    - More than 2 weeks of preoperative CPAP improved HTN, O₂ saturation, apneic events
    - Pulmonary HTN: in 20%–40% of patients with OSA
    - Preoperative serum bicarbonate predicts hypoxia in OSA
    - Chronic respiratory acidosis
    - Site of service (American Society of Anesthesiology consensus statement)
    - Ambulatory surgery under local/regional—lower risk
    - Avoid procedures requiring opioids—greater risk
    - Comorbid conditions must be optimized for outpatient surgery.

### Imaging and Special Studies

- **Radiation safety**
  - Should be considered for every fluoroscopic case
  - Increased radiation exposure associated with
    - Imaging of larger body parts
    - Positioning the extremity closer to the x-source
  - Restraints as last resort
  - Radiation safety
  - Family/friends
  - Medications for sedation: used with caution

### Other Basic Principles

#### Use of large C-arm rather than mini C-arm
- Factors to decrease the amount of radiation exposure
  - Minimizing exposure time
  - Using collimation to manipulate the x-ray beam
  - Use of protective shielding
  - Maximizing the distance between the surgeon and the radiation beam

**STOP-BANG scoring method**

<table>
<thead>
<tr>
<th>Every Yes answer = 1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring: Do you snore loudly (loud enough to be heard through closed doors)?</td>
</tr>
<tr>
<td>Tired: Do you often feel tired, fatigued, or sleepy during daytime?</td>
</tr>
<tr>
<td>Observed: Has anyone observed you stop breathing during your sleep?</td>
</tr>
<tr>
<td>Blood Pressure: Do you have or are you being treated for high blood pressure?</td>
</tr>
<tr>
<td>BMI more than 35?</td>
</tr>
<tr>
<td>Age older than 50 years?</td>
</tr>
<tr>
<td>Neck circumference greater than 40 cm?</td>
</tr>
<tr>
<td>Gender male?</td>
</tr>
</tbody>
</table>

5 or more = high risk for Obstructive Sleep Apnea
Initiate or continue CPAP machine
Avoid/minimize narcotics – maximize local blocks


- HTN, arrhythmias, CHF, cardiovascular disease, and metabolic syndrome
- Metabolic syndrome = obesity, hypertension, hypercholesterolemia, dyslipidemia, and insulin resistance
  - Avoidance of flat supine position; sitting position opens airway.

#### Malignant hyperthermia
  - **Autosomal dominant** genetic defect of T-tubule of sarcoplasmic reticulum
    - Ryanodine receptor defect (RYR1)
    - Dihydropyridine receptors (DHP)
  - **Triggered by volatile anesthetics and succinylcholine**
    - Creates an uncontrolled release of Ca²⁺
    - Sustained muscular contraction (masseter rigidity)
  - **Increased end-tidal CO₂**
  - **Earliest and most sensitive sign**
    - Mixed respiratory and metabolic alkalosis
  - **Hyperthermia is classic but occurs later.**
  - **Muscle damage**
    - Myoglobin from rhabdomyolysis can cause ARF
    - Elevated creatine kinase
    - Hyperkalemia can lead to ventricular arrhythmias.
  - **Treatment with dantrolene**
    - Decreases intracellular Ca²⁺
    - Stabilizes sarcoplasmic reticulum
  - **Treatment of high serum potassium**
  - **Hydration**
  - **Cooling**
• Utilizing mini C-arm whenever feasible (associated with minimal radiation exposure)
• Surgeon control of the C-arm

**Nuclear medicine**

- Bone scan (Table 1.37)
  - Technetium Tc 99m phosphate complexes
  - Reflect increased blood flow and metabolism (infection, trauma, neoplasia)
  - Absorbed onto hydroxyapatite crystals in bone
  - Whole-body views and more detailed (pinhole) views possible
  - Uses
    - Subtle or stress fractures
    - Avascular necrosis
    - Hyperperfused early
    - Increased uptake in reparative phase
    - Osteomyelitis
    - Also in conjunction with gallium citrate Ga 67 or indium In 111 scan
  - THA and TKA loosening
    - Especially femoral components
    - In conjunction with gallium scan to rule out infection
  - Phase studies
    - Three-phase (or even four-phase) studies
      - Help for reflex sympathetic dystrophy and osteomyelitis
      - First phase (blood flow, immediate)
      - Blood flow through the arterial system
      - Second phase (blood pool, 30 minutes)
      - Equilibrium of tracer throughout the intravascular volume
      - Third phase (delayed, 4 hours)
      - Displays sites of tracer accumulation
  - Gallium scan
    - Localizes in sites of inflammation and neoplasia
    - Exudation of labeled serum proteins
    - Difficult differentiating cellulitis from osteomyelitis
  - Indium scan
    - Labeled WBCs (leukocytes)
      - Collect in areas of inflammation
      - Do not collect in areas of neoplasia
    - Uses
      - Acute infections (e.g., osteomyelitis)
      - Possibly total joint arthroplasty (TJA) infections

**Indium scan**

- Labeled WBCs (leukocytes)
  - Collect in areas of inflammation
  - Do not collect in areas of neoplasia
- Uses
  - Acute infections (e.g., osteomyelitis)
  - Possibly total joint arthroplasty (TJA) infections

**Arthrography**

- Commonly used in association with advanced imaging (CT or MRI)
- Improves sensitivity of intraarticular soft tissue pathology (labral tear in shoulder, triangular fibrocartilage complex [TFCC], and intercarpal ligament tears in wrist)
- Also frequently used in pediatric population
- Hip
  - Aspiration for infection
  - Following reduction of developmental dysplasia of the hip (DDH)
  - Assessing deformity in Legg-Calvé-Perthes disease

**MRI**

- Excellent for evaluating soft tissues and bone marrow
  - Study of choice for evaluating knee ligamentous/meniscal injuries and shoulder cuff injuries
- Ineffective in evaluating trabecular bone and cortical bone
  - These tissues have virtually no hydrogen nuclei.
- Used to evaluate osteonecrosis, neoplasms, infection, and trauma
- Contraindications
  - Pacemakers
  - Cerebral aneurysm clips
  - Shrapnel or hardware, in certain locations
- Basic principles of MRI (Tables 1.38 through 1.41)
  - Radiophase frequencies on tissues in a magnetic field
  - Images in any desired plan
  - Nuclei with odd numbers of protons/neutrons (with a normally random spin) aligned parallel to a magnetic field

**Table 1.37  Nuclear Medicine Studies**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>USES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone scan</td>
<td>Subtle fractures&lt;br&gt;Avascular necrosis&lt;br&gt;Osteomyelitis&lt;br&gt;Total joint loosening&lt;br&gt;Osteochondritis</td>
<td>Three-phase scan useful for osteomyelitis, reflex sympathetic dystrophy, acute scaphoid fractures</td>
</tr>
<tr>
<td>Gallium</td>
<td>Inflammation&lt;br&gt;Neoplasms</td>
<td>Localizes in sites of inflammation&lt;br.Requires prolonged uptake</td>
</tr>
<tr>
<td>Indium (In 111)</td>
<td>Acute infections&lt;br&gt;Possible arthroplasty infections</td>
<td>Labeled WBC uptake in areas of infection</td>
</tr>
</tbody>
</table>

**Table 1.38  Magnetic Resonance Imaging Terminology**

<table>
<thead>
<tr>
<th>TERM</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Time constant of exponential growth of magnetism; T1 signal measures how rapidly a tissue gains magnetism</td>
</tr>
<tr>
<td>T2</td>
<td>Time constant of exponential decay of signal after an excitation pulse; a tissue with a long T2 signal (such as that with a high water content) maintains its signal (is bright on T2-weighted image)</td>
</tr>
<tr>
<td>T2*</td>
<td>Similar to T2 but includes the effects of magnetic field homogeneity</td>
</tr>
<tr>
<td>TR</td>
<td>Time to repetition; the time between successive excitation pulses; short TR &lt;80 ms, long TR &gt;80 ms</td>
</tr>
<tr>
<td>TE</td>
<td>Time to echo; the time that an echo is formed by the refocusing pulse; short TE &lt;1000 ms, long TE &gt;1000</td>
</tr>
<tr>
<td>NEX</td>
<td>Number of excitations; higher NEX results in decreased noise with better images</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>Spin-echo</td>
<td>A commonly used pulse sequence</td>
</tr>
<tr>
<td>FSE</td>
<td>Fast spin-echo; a type of pulse sequence</td>
</tr>
<tr>
<td>GRE</td>
<td>Gradient-recalled echo; a type of pulse sequence</td>
</tr>
</tbody>
</table>
• Field strength: 0.5–15 T (1 T = 10,000 G)
  • 3.0 T has nine times greater proton energy than 1.5 T
• Nuclear magnetic moments of these particles are deflected by radiofrequency pulses; deflection results in an image.
• The use of surface coils decreases the signal-to-noise ratio.
  • Body coils are used for large joints
  • Smaller coils are available
• Sequences developed to demonstrate the differences in T1 and T2 relaxation between tissues
  • Dark on T1- and bright on T2-weighted images
    • Water
    • Cerebrospinal fluid
    • Acute hemorrhage
• Tissues showing similar intensity on both T1- and T2-weighted images:
  • Dark: cortical bone, rapidly flowing blood, fibrous tissue
  • Gray: muscle and hyaline cartilage
  • Bright: fatty tissue, nerves, slowly flowing (venous) blood, bone marrow

**T1-weighted images best for demonstrating anatomic structure**
**T2-weighted images best for contrasting normal and abnormal tissues**
• Magic angle phenomenon:
  • Tendon or ligament tissue oriented near 55 degrees to the field produces bright T1-weighted images.
  • False appearance of pathologic process
  • Most common in shoulder, ankle, knee
• Techniques for identifying contrast between fluid and nonfluid elements (e.g., bone, fat)
  • STIR imaging
  • Fat-suppressed T2-weighted imaging
• Specific applications
  • Osteonecrosis
    • Highest sensitivity and specificity for early detection
    • Detects early marrow necrosis
    • Detects ingrowth of vascularized mesenchymal tissue
    • Specificity of 98% and high reliability for estimating age and extent of disease
    • Diseased marrow dark on T1-weighted images
    • Allows direct assessment of overlying cartilage
  • Infection and trauma
    • Excellent sensitivity to increased free water
    • Shows areas of infection and fresh hemorrhage
    • Dark on T1-weighted images, bright on T2-weighted images
    • Excellent (accurate and sensitive) for occult fractures
    • Particularly in hip in elderly patients
  • Neoplasms
    • MRI has many applications in the study of primary and metastatic bone tumors.
    • Primary tumors are well demonstrated.
    • Particularly tumors in soft tissue (extraosseous and marrow)
    • Used in evaluating skip lesions and spinal metastases
    • Nuclear medicine study remains the procedure of choice for seeking metastatic foci in bone.
    • Demonstrates benign bony tumors
    • Typically bright on T1-weighted images and dark on T2-weighted images
    • Demonstrates malignant bony lesions
    • Often bright on T2-weighted images
    • Differential diagnosis is best made on the basis of plain radiographs.
  • Spine
    • Disc disease is well demonstrated on T2-weighted images.
    • Degenerated discs lose water.

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>APPEARANCE ON T1-WEIGHTED IMAGE</th>
<th>APPEARANCE ON T2-WEIGHTED IMAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical bone</td>
<td>Dark</td>
<td>Dark</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Dark</td>
<td>Bright</td>
</tr>
<tr>
<td>Ligaments</td>
<td>Dark</td>
<td>Dark</td>
</tr>
<tr>
<td>Fibrocartilage</td>
<td>Dark</td>
<td>Dark</td>
</tr>
<tr>
<td>Hyaline cartilage</td>
<td>Gray</td>
<td>Gray</td>
</tr>
<tr>
<td>Meniscus</td>
<td>Dark</td>
<td>Gray</td>
</tr>
<tr>
<td>Meniscal tear</td>
<td>Bright</td>
<td>Gray</td>
</tr>
<tr>
<td>Yellow bone marrow</td>
<td>Gray</td>
<td>Gray</td>
</tr>
<tr>
<td>(fatty-appendicular)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red bone marrow (hematopoietic-axial)</td>
<td>Gray</td>
<td>Gray</td>
</tr>
<tr>
<td>Marrow edema</td>
<td>Dark</td>
<td>Bright</td>
</tr>
<tr>
<td>Fat</td>
<td>Bright</td>
<td>Gray</td>
</tr>
<tr>
<td>Normal fluid</td>
<td>Dark</td>
<td>Bright</td>
</tr>
<tr>
<td>Abnormal fluid (pus)</td>
<td>Gray</td>
<td>Bright</td>
</tr>
<tr>
<td>Acute blood collection</td>
<td>Gray</td>
<td>Bright</td>
</tr>
<tr>
<td>Chronic blood collection</td>
<td>Gray</td>
<td>Gray</td>
</tr>
<tr>
<td>Muscle</td>
<td>Gray</td>
<td>Gray</td>
</tr>
<tr>
<td>Tendon</td>
<td>Dark</td>
<td>Bright</td>
</tr>
<tr>
<td>Intervertebral disc (central)</td>
<td>Gray</td>
<td>Bright</td>
</tr>
<tr>
<td>Intervertebral disc (peripheral)</td>
<td>Dark</td>
<td>Gray</td>
</tr>
</tbody>
</table>

**Table 1.39 Signal Intensities on Magnetic Resonance Imaging**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PATHOLOGIC FEATURES</th>
<th>EXAMPLES</th>
<th>MRI CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconversion</td>
<td>Yellow → red</td>
<td>Anemia, metastasis</td>
<td>↑ T1-weighted intensity</td>
</tr>
<tr>
<td>Marrow infiltration</td>
<td></td>
<td>Tumor, infection</td>
<td>↑ T1-weighted intensity</td>
</tr>
<tr>
<td>Myeloid depletion</td>
<td></td>
<td>Anemia, chemotherapy</td>
<td>↑ T1-weighted intensity</td>
</tr>
<tr>
<td>Marrow edema</td>
<td></td>
<td>Trauma, complex regional pain syndrome</td>
<td>↑ T1-weighted intensity, ↑ T2-weighted intensity</td>
</tr>
<tr>
<td>Marrow ischemia</td>
<td></td>
<td>Osteonecrosis</td>
<td>↑ T1-weighted intensity</td>
</tr>
</tbody>
</table>

1, increased; 1, decreased.

**Table 1.41 Magnetic Resonance Imaging Changes of Meniscal Disease**

<table>
<thead>
<tr>
<th>DISEASE GROUP</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Globular areas of hyperintense signal</td>
</tr>
<tr>
<td>II</td>
<td>Linear hyperintense signal</td>
</tr>
<tr>
<td>III</td>
<td>Linear hyperintense signal that communicates with the meniscal surface (tears)</td>
</tr>
<tr>
<td>IV</td>
<td>Vertical longitudinal tear/truncation</td>
</tr>
</tbody>
</table>

- Appear dark on T2-weighted images
- Extent of herniation of discs is also well shown.
- Recurrent disc herniation is best diagnosed with gadolinium MRI scan.
- Differentiation from scar
  - T1-weighted image
    - Scar: decreased signal
    - Free fragment: increased signal
    - Extruded disc: decreased signal
  - T2-weighted image
    - Scar: increased signal
    - Free fragment: increased signal
    - Extruded disc: decreased signal
- MRI is most sensitive for diagnosing early discitis.
- Decreased signal on T1-weighted images, increased signal on T2-weighted images
- Bone marrow disorders
- Best demonstrated by MRI (poor specificity) (see Table 1.40)

**Other imaging studies**

- Computed tomography
  - Demonstrates details of bony anatomy better than any other study
  - Hounsfield units used to identify tissue types
    - −100 HU = air
    - −100–0 HU = fat
    - 0 HU = water
    - 100 HU = soft tissue
    - 1000 HU = bone
  - In spine, shows herniated nucleus pulposus better than myelography alone
    - CT may be helpful differentiating disc herniation from scar
    - IV contrast material is taken up in scar tissue but not in disc tissue.
  - Frequently used with contrast material
    - Arthrographic CT, myelographic CT
    - CT digital radiography (CT scanography)
    - Accurate demonstration of leg length discrepancy with minimal radiation exposure
    - Particularly when joint contractures exist (lateral scanography)
  - Images distorted by metal implants

- Ultrasonography: uses continue to expand
  - Shoulder: evaluation of rotator cuff tears
  - Hip
    - Diagnosis and follow-up of DDH
    - Dynamic examination of femoroacetabular impingement
  - Knee
    - Determination of articular cartilage thickness
    - Identification of intraarticular fluid
    - Soft tissue masses

- Hematoma
- Tendon rupture
- Abscesses
- Foreign body location
- Intraspinal disorders in infants
- Intraarticular injections

- Myelography
  - More invasive than MRI but shows excellent detail
  - Useful in patients with contraindications to MRI
  - Useful in failed back (surgery) syndrome
  - Can be used with other studies such as CT

- Discography
  - Use controversial
  - Helpful for evaluating symptomatic disc degeneration
  - Pathologic discs: reproduction of pain with injection and characteristic changes on discograms
  - Commonly used with CT

- Measurement of bone density (noninvasive)
  - Single-photon absorptiometry
    - Cortical bone density is inversely proportional to quantity of photons passing through it.
    - Radioisotope iodide 125 (\(^{125}\text{I}\)) emits a single energy beam of photons.
      - \(^{125}\text{I}\) passes through bone.
      - A sodium iodide scintillation counter detects the transmitted photons.
    - Denser bone attenuates the photon beam.
      - Fewer photons reach the scintillation counter.
  - Best used in the appendicular skeleton
    - Radius: diaphysis or distal metaphysis
    - Findings are unreliable in the axial skeleton
    - Soft tissue depth alters the beam.
  - Dual-photon absorptiometry
    - Also an isotope-based method
    - Allows for measurement of the axial skeleton and the femoral neck
    - Accounts for soft tissue attenuation
  - Quantitative CT
    - Preferred for measurement of trabecular bone density
    - Trabecular bone is at greatest risk for early metabolic changes
    - Simultaneous scanning of phantoms of known density
      - Creating a standard calibration curve
      - Accuracy within 5%–10%
    - Radiation dose higher than that for DEXA
  - DEXA
    - Most accurate and reliable for predicting fracture risk
    - Radiation dose lower than that for quantitative CT
    - Measures bone mineral content and soft tissue components

- Electrodiagnostic studies

- Nerve conduction studies
  - Evaluation of peripheral nerves
  - Nerve impulses stimulated and recorded by surface electrodes
    - Allows calculation of conduction velocity
  - Measures latency (time from stimulus onset to response) and response amplitude
  - Late responses (F wave, H reflex) allow evaluation of proximal lesions.
  - Impulse travels to the spinal cord and returns

- Electromyography
• Use of intramuscular needle electrodes to evaluate muscle units
• Used to evaluate denervation
  • Fibrillations; earliest sign usually at 4 weeks
  • Sharp waves
  • Abnormal recruitment pattern
• Interpretation
  • Peripheral nerve entrapment syndromes
  • Distal motor and sensory latencies more than 35 m/sec
  • Nerve conduction velocities less than 50 m/sec
  • Changes over a distinct interval (Table 1.42)

Newton's laws
• First law: inertia
  • If the net external force ($F$) acting on a body is zero, the body remains at rest or moves with a constant velocity.
  • This law allows static analysis: $\Sigma F = 0$ (sum of external forces = zero)
• Second law: acceleration
  • Acceleration ($a$) of an object of mass ($m$) is directly proportional to the force ($F$) applied to the object:
  $$F = ma$$
  • This law is used in dynamic analysis.
• Third law: reactions
  • For every action (force), there is an equal and opposite reaction (force).
  • This law leads to free-body analysis.
  • This law also assists in the study of interacting bodies.

BIOMATERIALS AND BIOMECHANICS

Basic concepts

Definitions
• Biomechanics—science of forces, internal or external, on the living body
• Statics—action of forces on rigid bodies in a system in equilibrium
• Dynamics—bodies that are accelerating and the related forces
  • Kinematics—study of motion (displacement, velocity, and acceleration) without reference to forces
  • Kinetics—relates the effects of forces to motion

Principal quantities
• Basic quantities—described by International System of Units (SI); metric system
  • Length (m), mass (kg), time (sec)
• Derived quantities: derived from basic quantities
  • Velocity
    • Time rate of change of displacement (meters/second)
    • Rate of translational displacement: linear velocity
    • Rate of rotational displacement: angular velocity
  • Acceleration
    • Time rate of change of velocity (m/sec$^2$)
    • Can also be linear or angular
  • Force
    • Action causing acceleration of a mass (body) in a certain direction
    • Unit of measure: newton (N) = kg • m/sec$^2$

Scalar and vector quantities
• Scalar quantities
  • Have magnitude but no direction
  • Examples: volume, time, mass, and speed (not velocity)
• Vector quantities
  • Have magnitude and direction
  • Examples: force and velocity
  • Vectors have four characteristics
    • Magnitude (length of the vector)
    • Direction (head of the vector)
    • Point of application (tail of the vector)
    • Line of action (orientation of the vector)
  • Vectors can be added, subtracted, and split into components (resolved)
  • Resultant of two vectors: principle of “parallelogram of forces”

Free-body analysis
• Forces, moments, and free-body diagrams to analyze the action of forces on bodies
• Force
  • A mechanical push or pull (load) that causes external (acceleration) and internal (strain) effects

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>LATENCY</th>
<th>CONDUCTION VELOCITY</th>
<th>EVOKED RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal study</td>
<td>Normal</td>
<td>Upper extremities: &gt;45 m/sec; lower extremities: &gt;40 m/sec</td>
<td>Biphasic</td>
</tr>
<tr>
<td>Axonal neuropathy</td>
<td>Increased</td>
<td>Normal or slightly decreased</td>
<td>Prolonged, decreased amplitude</td>
</tr>
<tr>
<td>Demyelinating neuropathy</td>
<td>Normal</td>
<td>Decreased (10%–50%)</td>
<td>Normal or prolonged, with decreased amplitude</td>
</tr>
<tr>
<td>Anterior horn cell disease</td>
<td>Normal</td>
<td>Normal (rarely decreased)</td>
<td>Normal or polyphasic, with prolonged duration and decreased amplitude</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased amplitude; may be normal</td>
</tr>
<tr>
<td>Neuapraxia:</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Proximal to lesion</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Distal to lesion</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Axonotmesis:</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Proximal to lesion</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Distal to lesion</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Neurotmesis:</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Other important basic concepts

- Force vectors ($F$): can be split into independent components for analysis
  - Usually in the $x$ and $y$ directions ($F_x$, $F_y$).
  - With angle ($\theta$) between $F_x$ and $F_y$.
  - A normal force is perpendicular to the surface on which it acts.
  - A tangential force is parallel to the surface.
  - A compressive force shrinks a body in the direction of the force.
  - A tensile force elongates a body.

- Moment ($M$)
  - Rotational effect of a force
  - Moment = force ($F$) multiplied by the perpendicular distance (the moment arm or lever arm = $d$) from point of rotation:
    $$ M = F \times d $$
  - Torque is a moment from a force perpendicular to the long axis of a body, causing rotation.
  - A bending moment is from a force parallel to the long axis.
  - The mass moment of inertia is the resistance to rotation.
  - Product of mass times the square of the moment arm:
    $$ I = m \times d^2 $$
  - Affects angular acceleration

- Free-body diagram
  - A free-body diagram is a sketch of a body (or segments) isolated from other bodies that shows all forces acting on it.
  - The weight of each object acts through its center of gravity.
  - Center of gravity in the human body is just anterior to S2.

Finite element analysis

- Complex geometric forms and material properties are modeled.
- A structure is modeled as a finite number of simple geometric forms.
  - Typically triangular or trapezoidal elements
- A computer matches forces and moments between neighboring elements.
- Finite element analysis is often used to estimate internal stresses and strains.
  - Example: stress/strain at bone-implant interface

Biomaterials

- Strength of materials
  - Study of relations between externally applied loads and resulting internal effects
  - Loads
    - Forces acting on a body
    - Compression, tension, shear, and torsion
  - Deformations
    - Temporary (elastic) or permanent (plastic) change in shape
  - Elasticity—ability to return to resting length after undergoing lengthening or shortening
  - Extensibility—ability to be lengthened
  - Stress
    - Intensity of internal force
      - Stress = force/area
      - Internal resistance of a body to a load
    - Unit of measure: pascal (Pa) = N/m²
  - Normal stresses
    - Compressive or tensile
    - Perpendicular to the surfaces on which they act
  - Shear stresses
    - Parallel to the surfaces on which they act
    - Cause a part of a body to be displaced in relation to another part
  - Stress differs from pressure:
    - Pressure is the distribution of an external force to a solid body.
    - However, they share the same definition (force/area) and unit of measure (Pa).

Strain

- Relative measure of deformation (six components) resulting from loading
  - Strain = change in length/original length
  - Can also be normal or shear
  - Strain is a proportion; it has no units.
  - Strain rate
    - Strain divided by time load is applied (units = sec⁻¹).
    - Hooke’s law: stress is proportional to strain up to a limit.
    - The proportional limit
    - Within the elastic zone
  - Young’s modulus of elasticity ($E$)
    - Measure of material stiffness
      - Also a measure of the material’s ability to resist deformation in tension
      - $E = \text{stress/strain}$
      - $E$ is the slope in the elastic range of the stress-strain curve.
Stress-strain curve. $E$, Young’s modulus of elasticity.

- The critical factor in load-sharing capacity
- Linearly perfect elastic material
  - A straight stress-strain curve to the point of failure
  - *Modulus = stress at failure (ultimate stress) divided by strain at failure (ultimate strain)*
- $E$ is unique for every type of material
  - A material with a higher $E$ can withstand greater forces than can material with a lower $E$.
- Shear modulus
  - Ratio of shear stress to shear strain
  - A measure of stiffness
  - Unit of measure: pascal (Pa)
- Stress-strain curve (Fig. 1.60)
  - Derived by loading a body and plotting stress versus strain
    - The curve’s shape varies by material.
    - Proportional limit—transition point at which stress and strain are no longer proportional
    - The material returns to its original length when stress is removed: elastic behavior.
  - Elastic limit (yield point)
    - This is the transition point from elastic to plastic behavior.
    - Beyond this point, the material’s structure is irreversibly changed.
    - The elastic limit equals 0.2% strain in most metals.
  - Plastic deformation—irreversible change after load is removed
    - Occurs in the plastic range of the curve
    - After the elastic limit, before the breaking point
  - Ultimate strength—maximum strength obtained by the material
  - Breaking point—point at which the material fractures
    - Ductile—if deformation between elastic limit and breaking point is large
    - Brittle—if deformation between elastic limit and breaking point is small
  - Strain energy (toughness)
    - Capacity of material (e.g., bone) to absorb energy
    - Area under the stress-strain curve
    - Total strain energy = recoverable strain energy (resilience) + dissipated strain energy
    - A measure of the toughness of material
    - Ability to absorb energy before failure

### Material definitions
- Brittle materials (e.g., PMMA)
  - Stress-strain curve is linear up to failure.
  - These materials undergo only recoverable (elastic) deformation before failure.
  - They have little or no capacity for plastic deformation.
- Ductile materials (e.g., metal)
  - These materials undergo large plastic deformation before failure.
  - Ductility is a measure of post-yield deformation.
- Viscoelastic materials (e.g., bone and ligaments)
  - Stress-strain behavior is time-rate dependent.
    - Depends on load magnitude and rate at which the load is applied
  - A function of internal friction
  - Exhibit both fluid (viscosity) and solid (elasticity) properties
  - Modulus increases as strain rate increases.
  - Exhibit hysteresis
    - Loading and unloading curves differ.
    - Energy is dissipated during loading.
  - Most biologic tissues exhibit viscoelasticity.
- Isotropic materials
  - Mechanical properties are the same for all directions of applied load (e.g., as with a golf ball).
- Anisotropic materials
  - Mechanical properties vary with the direction of the applied load.
    - Example: bone is stronger with axial load than with radial load.
- Homogeneous materials
  - Have a uniform structure or composition throughout
- Rigidity
  - Bending rigidity of a rectangular structure:
    - Proportional to the base multiplied by the height cubed:
      \[ bh^{3/12} \]
  - Bending rigidity of a cylinder
  - Related to the fourth power of the radius
  - Examples: intramedullary nails, half-pins

### Metals
- Fatigue failure
  - Occurs with cyclic loading at stress below ultimate tensile strength
  - Depends on magnitude of stress ($S$) and number of cycles ($n$)
- Endurance limit
  - Maximum stress under which the material will not fail regardless of number of loading cycles
  - If the stress is below this limit, the material may be loaded cyclically an infinite number of times ($>10^6$ cycles) without breaking.
  - Above this limit, fatigue life is expressed by the $S$-$n$ curve:
- Creep (cold flow)
  - Progressive deformation response to constant force over an extended period
  - Sudden stress followed by constant loading causes continued deformation.
  - Can produce permanent deformity
  - May affect mechanical function (e.g., in TJA)
- Corrosion (Table 1.43)
  - Chemical dissolving of metals
**Table 1.43 Types of Corrosion**

<table>
<thead>
<tr>
<th>CORROSION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galvanic</td>
<td>Dissimilar metals; electrochemical destruction</td>
</tr>
<tr>
<td>Crevice</td>
<td>Occurs in fatigue cracks with low ( O_2 ) tension</td>
</tr>
<tr>
<td>Stress</td>
<td>Occurs in areas with high stress gradients</td>
</tr>
<tr>
<td>Fretting</td>
<td>From small movements abrading outside layer</td>
</tr>
<tr>
<td>Other</td>
<td>For example, inclusion, intergranular</td>
</tr>
</tbody>
</table>

*Metals such as 316L stainless steel and cobalt-chromium-molybdenum (Co-Cr-Mo) alloy produce galvanic corrosion.*

- May occur in the body’s high-saline environment
- Stainless steel (type 316L)
- The metal most susceptible to both crevice corrosion and galvanic corrosion
- Risk of galvanic corrosion highest between 316L stainless steel and cobalt-chromium (Co-Cr) alloy
- Modular components of THA
- Direct contact between similar or dissimilar metals at the modular junctions
- Results in corrosion products
  - Examples: metal oxides, metal chlorides
- Corrosion can be decreased in the following ways:
  - Using similar metals
  - Proper implant design
  - Passivation by an adherent oxide layer
  - Effectively separates metal from solution
  - Example: stainless steel coated with chromium oxide

- Types of metals
- Orthopaedic implants
  - Three types of alloys: steel (iron-based), cobalt-based, titanium-based
  - 316L stainless steel
    - Iron-carbon, chromium, nickel, molybdenum, manganese
    - Nickel: increases corrosion resistance and stabilizes molecular structure
    - Chromium: forms a passive surface oxide, improving corrosion resistance
    - Molybdenum: prevents pitting and crevice corrosion
    - Manganese: improves crystalline stability
  - “L” — low in carbon: greater corrosion resistance
- Cobalt alloys
  - Cobalt-chromium-molybdenum (Co-Cr-Mo)
    - 65% cobalt, 35% chromium, 5% molybdenum
  - Special forging process
  - Nickel may be added to improve ease of forging
  - Greater ultimate strength than titanium
  - Ion release
    - Co-Cr: macrophage proliferation and synovial degeneration
    - Ions excreted through the kidneys
- Titanium alloy (Ti-6Al-4V)
  - Poor resistance to wear (notch sensitivity)
  - Particulate may incite a histiocytic response.
  - The relationship between titanium and neoplasms is uncertain.

**FIG. 1.61** Comparison of Young’s modulus (relative values, not to scale) for various orthopaedic materials. \( \text{Al}_2\text{O}_3 \), Alumina; Co-Cr-Mo, cobalt-chromium-molybdenum; PMMA, polymethylmethacrylate.

- Polishing, passivation, and ion implantation improve its fatigue properties.
- Titanium is extremely biocompatible
- Rapidly forms an adherent oxide coating (self-passivation); decreases corrosion
- Most closely emulates axial and torsional stiffnesses of bone
- High yield strength
- Tantalum—passive material designed to elicit a response (bone ingrowth)
- Surface oxide layer as barrier to corrosion
- Used as augmentation of cancellous defects
- Stiffness (\( E \)) differences (Fig. 1.61)

**Nonmetal materials**

- Polyethylene (discussed in Chapter 5, Adult R reconstruction)
- PMMA (bone cement)
  - Used for fixation and load distribution for implants
  - Acts as a grout, not an adhesive
  - Mechanically interlocks with bone
  - **Reaches ultimate strength within 24 hours**
  - Can be used as an internal splint for the patient with poor bone stock
  - PMMA can be used as a temporary internal splint until the bone heals.
  - If bone fails to heal, PMMA will ultimately fail.
  - Poor tensile and shear strength
  - Is strongest in compression and has a low \( E \)
  - Not as strong as bone in compression
  - Reducing voids (porosity) increases cement strength and decreases cracking.
  - Vacuum mixing, centrifugation, good technique
  - Cement failure often caused by microfracture and fragmentation.
  - Insertion can lead to a precipitous drop in BP.
  - Wear particles can incite a macrophage response
  - Leads to prosthesis loosening

- Silicones
- Polymers for replacement in non–weight-bearing joints
- Poor strength and wear capabilities
- Frequent synovitis with extended use

- Ceramics
- Metallic and nonmetallic elements bonded ionically in a highly oxidized state
Basic Sciences

• Good insulators (poor conductors)
• Biostable (inert) crystalline materials such as Al₂O₃ (alumina) and ZrO₂ (zirconium dioxide)
• Bioactive (degradable) noncrystalline substances such as bioglass
  • Typically brittle (no elastic deformation)
  • High modulus (E)
  • High compressive strength
  • Low tensile strength
  • Low yield strain
  • Poor crack resistance characteristics
    • Low resistance to fracture
  • Best wear characteristics, with polyethylene and a low oxidation rate
  • High surface wettability and high surface tension
  • Highly conducive to tissue bonding
  • Less friction and diminished wear (“smooth surface”)
  • Small grain size allows an ultrasmooth finish.
  • Less friction
  • Calcium phosphates (e.g., hydroxyapatite) may be useful as coatings (plasma sprayed) to increase attachment strength and promote bone healing.
  
  Mechanical properties of tissue

  • Bone
    • Composite of collagen and hydroxyapatite
      • Collagen: low E, good tensile strength, poor compressive strength
      • Calcium apatite: stiff, brittle, good compressive strength
  • Anisotropic
    • Strongest in compression
    • Weakest in shear
    • Intermediate in tension
  • Resists rapidly applied loads better than slowly applied loads
  • Cancellous bone is 25% as dense, 10% as stiff, and 500% as ductile as cortical bone.
  • Cortical bone excellent at resisting torque.
  • Cancellous bone good at resisting compression and shear.
  • Bone is dynamic.
    • Able to self-repair
    • Changes with aging: stiffer and less ductile
    • Changes with immobilization: weaker
  • Bone aging
    • To offset loss in material properties, bone remolds to increase inner and outer cortical diameters.
    • Area moment of inertia increases.
      • Bending stresses decrease.
  • Stress concentration effects
    • Occur at defect points within bone or at implant-bone interface (stress risers)
    • Reduce overall loading strength
  • Stress shielding by load-sharing implants
    • Induces osteoporosis in adjacent bone
      • Decreases normal physiologic bone stresses
    • Common under plates and at the femoral calcar in high-riding THA
    • A hole measuring 20%–30% of bone diameter reduces strength up to 50%.
      • Regardless of whether it is filled with a screw
      • Area returns to normal 9–12 months after screw removal.

  • Cortical defects can reduce strength 70% or more.
  • Oval defects less than rectangular defects
  • Smaller stress riser (concentration)

  Fracture
  • Type is based on mechanism of injury.
    • Tension: typically transverse and perpendicular to load and bone axis
    • Compression: crush fracture
    • Shear
      • Commonly around joints
      • Load parallel to the bone surface
      • Fracture parallel to the load
  • Bending
    • Eccentric loading or direct blows
    • Begins on the tension side of the bone
    • Continues transversely/obliquely
    • May bifurcate to produce a butterfly fragment
    • High-velocity bending: produces comminuted butterfly fracture
    • Four-point bending: produces segmental fracture
  • Torsion
    • Shear and tensile stresses around the longitudinal axis
    • Most likely to result in a spiral fracture
    • Torsional stresses proportional to the distance from the neutral axis to the periphery of a cylinder
    • Greatest stresses in a long bone under torsion are on the outer (periosteal) surface
  • Comminution
    • A function of the amount of energy transmitted to bone

  Ligaments and tendons
  • Can sustain 5%–10% tensile strain before failure.
    • In contrast, bone can sustain only 1%–4% tensile strain.
    • Failure commonly results from tension rupture of fibers and shear failure among fibers.
    • Most ligaments can undergo plastic strain to the point that function is lost but structure remains in continuity.
  • Articular cartilage
    • Ultimate tensile strength is only 5% that of bone.
    • E is only 0.1% that of bone.
    • However, because of its viscoelastic properties, is well suited for compressive loading.
  • Is biphasic
    • Solid phase depends on structural matrix.
    • Fluid phase depends on deformation and shift of water within solid matrix.
    • Relatively soft and impermeable solid matrix requires high hydrodynamic pressure to maintain fluid flow.
    • Significant support provided by the fluid component
    • Stress-shielding effect on the matrix

  Metal implants
  • Screws
    • Pitch: distance between threads
    • Lead: distance advanced in one revolution
    • Root diameter: minimal/inner diameter is proportional to tensile strength
    • Outer diameter: determines holding power (pullout strength)
- To maximize pullout strength
  - Large outer diameter
  - Small root diameter
  - Fine pitch
- Plates
  - Strength varies with material and moment of inertia.
  - **Bending stiffness is proportional to the third power of the thickness** ($t^3$).
    - Doubling thickness increases bending stiffness eightfold.
- Plates are load-bearing devices.
  - Most effective on a fracture’s tension side
- Types include:
  - Static compression
  - Dynamic compression
    - Example: tension band plate
  - Neutralization
  - Resists torsion
  - Buttress
    - Protects bone graft
    - Stress concentration at open screw holes can lead to implant failure.
  - Blade
    - Increased resistance to torsional deformation
  - Locking
    - Absorb axial forces transmitted from screws
    - Do not require compression to bone; preserve periosteal blood supply
    - Biomechanical advantages for osteoporotic fractures without cortical contact
  - Hybrid locking
    - Both nonlocked and locked screws are used.
    - Nonlocked screws assist in reduction.
    - Locked screws create a fixed-angle device or can be used in patients with osteoporosis.
  - **Bicortical locked screws provide increased strength in torsion compared with unicortical locked screws.**
- Intramedullary nails
  - Load-sharing devices
  - Require high polar moment of inertia to maximize torsional rigidity and strength
  - Mechanical characteristics
    - Torsional rigidity
      - Amount of torque needed to produce a unit angle of torsional deformation
      - Depends on both material properties (shear modulus) and structural properties (polar moment of inertia)
    - Bending rigidity
      - Amount of force required to produce a unit amount of deflection
      - Depends on both material properties (elastic modulus) and structural properties (area moment of inertia, length)
  - **Related to the fourth power of the nail’s radius**
    - Increasing nail diameter by 10% increases bending rigidity by 50%.
    - Better at resisting bending forces than rotational forces
  - Reaming
    - Allows greater torsional resistance
  - Larger contact area
  - A larger nail; increased rigidity and strength
  - Unslotted nails
    - Smaller diameter
    - Stronger fixation
      - At the expense of flexibility
      - Increased torsional stiffness: greatest advantage of closed-section nails over slotted nails
  - Intramedullary nail insertion for femoral shaft fracture
    - Hoop stresses are lowest for a slotted titanium alloy nail with a thin wall
    - Posterior starting points decrease hoop stresses and iatrogenic comminution of fractures
  - Implant failure is more common with smaller-diameter unreamed nails

### External fixators
- Conventional external fixators
  - Fracture reduction is the most important factor for stability of fixation with external fixation.
  - Other factors to enhance stability (rigidity) include
    - Larger-diameter pins (second most important factor)
    - Additional pins
    - Decreased bone-rod distance
    - Pins in different planes
    - Pins separated by more than 45 degrees
    - Increased mass of the rods or stacked rods
    - A second rod in the same plane increases resistance to bending.
    - Rods in different planes
    - Increased spacing between pins
    - Placement of central pins closer to the fracture site
    - Placement of peripheral pins farther from the fracture site (near-near, far-far).
- Circular (Ilizarov) external fixators
  - Thin wires (usually 1.8 mm in diameter)
  - Fixed under tension (usually between 90 and 130 kg)
  - Circular rings
  - Half-pins may also be used.
    - Offer better purchase in diaphyseal (not metaphyseal) bone
  - Optimum orientation of implants on the ring
    - At a 90-degree angle to each other
    - Maximizes stability
    - A 90-degree angle not always possible
    - Anatomic constraints such as neurovascular structures
  - **Bending stiffness of frame**
    - Independent of the loading direction
    - Because the frame is circular
  - Each ring should have at least two implants.
    - Wires or half-pins may be used.
    - The construct is most stable when an olive wire and a half-pin are at a 90-degree angle to each other on a ring.
  - Two wires are used on a ring.
    - One wire should be superior to the ring and one inferior.
    - Tensioned wires on the same side can cause the ring to deform.
  - Factors that enhance stability of circular external fixators
- Larger-diameter wires (and half-pins)
- Decreased ring diameter
- Use of olive wires
- Additional wires or half-pins (or both)
- Wires (or half-pins or both) crossing at a 90-degree angle
- Increased wire tension (up to 130 kg)
- Placement of the two central rings close to the fracture site
- Decreased spacing between adjacent rings
- Increased number of rings

Joint arthroplasty implants: discussed in Chapter 5, Adult Reconstruction chapter

### Biomechanics

#### General definitions
- Degrees of freedom
  - Rotations and translations each occur in the x, y, and z planes.
  - Thus six parameters, or degrees of freedom, describe motion.
- Translations may be relatively insignificant for many joints.
  - Are often ignored in biomechanical analyses
- Joint reaction force (R)
  - R is the force within a joint in response to forces acting on the joint.
  - Both intrinsic and extrinsic
  - Muscle contraction about a joint: the major contributing factor
  - R is correlated with predisposition to degenerative changes.
- Joint contact pressure (stress) can be minimized by
  - Decreasing R
  - Increasing contact area
- Coupled forces—rotation about one axis causes obligatory rotation about another axis (occurs in some joints).
  - Such movements (and associated forces) are coupled.
- Example: lateral bending of the spine accompanied by axial rotation
- Joint congruence
  - Related to the fit of two articulating surfaces
  - A necessary condition for joint motion
  - Can be evaluated radiographically
  - High congruence increases joint contact area
  - Low congruence decreases joint contact area
  - Movement out of a position of congruence increases stress in cartilage.
  - Allows less contact area for distribution of joint reaction force
  - Predisposes the joint to degeneration
- Instant center of rotation
  - Point about which a joint rotates
  - In some joints (knee), the instant center changes during the arc of motion, following a curved path.
  - Effect of joint translation and morphologic features
  - It normally lies on a line perpendicular to the tangent of the joint surface at all points of contact.
- Rolling and sliding (Fig. 1.62)
  - During motion, almost all joints roll and slide to remain in congruence.
  - Pure rolling:
    - Instant center of rotation is at the rolling surfaces.
    - Contacting points have zero relative velocity.
    - No “slipping” of one surface on the other
  - Pure sliding
    - Occurs with pure translation or rotation about a stationary axis
    - No angular change in position
    - No instant center of rotation
    - “Slipping” of one surface on the other
- Friction and lubrication
  - Friction: resistance between two objects as one slides over the other
  - Not a function of contact area
  - Coefficient of friction: 0 = no friction
  - Lubrication: decreases resistance between surfaces
  - Articular surfaces, lubricated with synovial fluid, have a coefficient of friction 10 times better than that of the best synthetic systems.
  - Coefficient of friction for human joints: 0.002–0.04
  - Coefficient of friction for metal-on-UHMWPE (ultra-high-molecular-weight polyethylene) joint arthroplasty: 0.05–0.15
  - Not as good as that of human joints
- Elastohydrodynamic lubrication
  - Primary lubrication mechanism for articular cartilage during dynamic function

### Hip biomechanics

#### Kinematics
- ROM (Table 1.44)
• Instant center
  • Simultaneous triplanar motion for this ball-and-socket joint makes analysis impossible.

• Kinetics
  • Joint reaction force (R) in the hip can reach three to six times body weight (W).
  • Primarily as a result of contraction of the muscles crossing the hip
  • Decreases with cane in contralateral hand

• Other considerations
  • Stability
    • Deep-seated ball-and-socket joint is intrinsically stable.
  • Sourcil
    • Condensation of subchondral bone under superomedial acetabulum
    • R is maximal at this point
  • Gothic arch
    • Remodeled bone supporting the acetabular roof
    • Sourcil at its base
  • Neck-shaft angle
    • Varus angulation
      • Increases R
      • Increases shear across the neck
      • Leads to shortening of the lower extremity
      • Alters muscle tension resting length of the abductors
      • May cause a persistent limp
    • Valgus angulation
      • Increases R
      • Decreases shear
      • Neutral or valgus angulation better for THA
      • PMMA resists shear poorly
  • Arthrodesis (Fig. 1.63)
    • Position: 25–30 degrees of flexion, 0 degrees of abduction and rotation
    • External rotation is better than internal rotation.
  • If the implant is fused in abduction, the patient will lurch over the affected lower extremity with an excessive trunk shift.
  • This will later result in low back pain.
  • Effects
    • Increases oxygen consumption
    • Decreases gait efficiency to approximately 50% of normal
    • Increases transpelvic rotation of the contralateral hip

Knee biomechanics

Kinematics

• ROM
  • 10 degrees of extension (recurvatum) to 130 degrees of flexion
  • Functional ROM is nearly full extension to about 90 degrees of flexion.
  • 117 degrees: required for squatting and lifting
  • 110 degrees: required for rising from a chair after TKA
  • Rotation varies with flexion
    • At full extension, rotation is minimal.
    • At 90 degrees of flexion, ROM is 45 degrees of external rotation and 30 degrees of internal rotation.
  • Amount of abduction or adduction is essentially 0 degrees.

• A few degrees of passive motion are possible at 30 degrees of flexion.
• Knee motion is complex about a changing instant center of rotation.
• Polycentric rotation
• Excursions of 0.5 cm for the medial meniscus and 1.1 cm for the lateral meniscus are possible during a 120-degree arc of motion.

• Joint motion
  • Instant center traces a J-shaped curve about the femoral condyle.
  • Moves posteriorly with flexion
  • Flexion and extension involve both rolling and sliding.
  • Femur rotates internally (tibia rotates externally) during the last 15 degrees of extension
  • “Screw home” mechanism
  • Related to differences in radii of curvature for the medial and lateral femoral condyles and the musculature
  • Posterior rollback increases maximum knee flexion.
  • Tibiofemoral contact point moves posteriorly.
  • Normal rollback is compromised by PCL sacrifice of posterior cruciate ligament (PCL), as in some TKAs.
  • Axis of rotation of the intact knee is in the medial femoral condyle.
  • Patellofemoral joint has sliding articulation
  • Patella slides 7 cm caudally with full flexion.
  • Instant center is near the posterior cortex above the condyles.

• Kinetics
  • Knee stabilizers
    • Ligaments and muscles play the major stabilizing role (Table 1.45).
    • ACL
      • Typically subjected to peak loads of 170 N during walking
        • Up to 500 N with running
      • Ultimate strength in young patients: about 1750 N
      • Failures by serial tearing at 10%–15% elongation
    • PCL: sectioning increases contact pressures in the medial compartment and the patellofemoral joint.
  • Joint forces
    • Tibiofemoral joint
      • Knee joint surface loads
        • Three times body weight during level walking
        • Up to four times body weight with stair walking
      • Menisci
        • Help with load transmission
      • Bear one-third to one-half body weight
      • Removal increases contact stresses

### Table 1.44 Hip Biomechanics: Range of Motion

<table>
<thead>
<tr>
<th>MOTION</th>
<th>AVERAGE RANGE (DEGREES)</th>
<th>FUNCTIONAL RANGE (DEGREES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexion</td>
<td>115</td>
<td>90 (120 to squat)</td>
</tr>
<tr>
<td>Extension</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Abduction</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Adduction</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Internal rotation</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>External rotation</td>
<td>45</td>
<td>20</td>
</tr>
</tbody>
</table>
Basic Sciences

A few degrees of passive motion are possible at 30 degrees of flexion. Knee motion is complex about a changing instant center of rotation. Polycentric rotation.

Excursions of 0.5 cm for the medial meniscus and 1.1 cm for the lateral meniscus are possible during a 120-degree arc of motion.

Joint motion. Instant center traces a J-shaped curve about the femoral condyle. Moves posteriorly with flexion.

Flexion and extension involve both rolling and sliding. Femur rotates internally (tibia rotates externally) during the last 15 degrees of extension. “Screw home” mechanism related to differences in radii of curvature for the medial and lateral femoral condyles and the musculature.

Posterior rollback increases maximum knee flexion. Tibiofemoral contact point moves posteriorly. Normal rollback is compromised by PCL sacrifice of posterior cruciate ligament (PCL), as in some TKAs.

The intact knee is in the medial femoral condyle. Patellofemoral joint has sliding articulation. Patella slides 7 cm caudally with full flexion. Instant center is near the posterior cortex above the condyles.


Menisci. Help with load transmission. Bear one-third to one-half body weight. Removal increases contact stresses up to four times the load transfer to bone.

Quadriceps produces maximum anterior force on the tibia at 0–60 degrees of knee flexion. Patellofemoral joint.

Patella aids in knee extension. Increases the lever arm. Stress distribution.

Has the thickest cartilage in the entire body. Bears the greatest load. Bears half the body weight with normal walking.

FIG. 1.63 Recommended positions for arthrodesis of common joints. CMC, Carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.
• Bears seven times the body weight with squatting and jogging
• Loads proportional to ratio of quadriceps force to knee flexion
• In descending stairs, compressive force reaches two to three times body weight.
• Patellectomy
  • Length of the moment arm is decreased by width of patella: 30% reduction.
  • Power of extension is decreased by 30%.
• During TKA, the following factors enhance patella tracking
  • External rotation of the femoral component
  • Lateral placement of the femoral and tibial components
  • Medial placement of the patellar component
  • Avoidance of malrotation of the tibial component
  • These actions avoid internal rotation.

• Axes of the lower extremity (Fig. 1.64)
  • Mechanical axis of the lower extremity
    • Center of femoral head to center of ankle
    • Normally passes just medial to the medial tibial spine
  • Vertical axis
    • From the center of gravity to the ground
  • Anatomic axes
    • Along the shafts of the femur and tibia
    • Where these axes intersect at the knee, valgus angle is normal.
  • Mechanical axis of the femur
    • From center of the femoral head to center of the knee
  • Mechanical axis of the tibia
    • From center of the tibial plateau to center of the ankle
  • Relationships
    • Mechanical axis of the lower extremity is in 3 degrees of valgus angulation from the vertical axis.
    • Anatomic axis of the femur is in 6 degrees of valgus angulation from the mechanical axis.
    • Nine degrees versus the vertical axis
    • Anatomic axis of the tibia is in 2–3 degrees of varus angulation from the mechanical axis.
• Arthrodesis (see Fig. 1.63)
  • Position: 0 to 7 degrees of valgus angulation, 10 to 15 degrees of flexion

### Table 1.45 Knee Stabilizers

<table>
<thead>
<tr>
<th>DIRECTION</th>
<th>STRUCTURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial</td>
<td>Superior MCL (primary), joint capsule, medial meniscus, ACL/PCL</td>
</tr>
<tr>
<td>Lateral</td>
<td>Joint capsule, IT band, LCL (middle), lateral meniscus, ACL/PCL (90 degrees)</td>
</tr>
<tr>
<td>Anterior</td>
<td>ACL (primary), joint capsule</td>
</tr>
<tr>
<td>Posterior</td>
<td>PCL (primary), joint capsule; PCL tightens with internal rotation</td>
</tr>
<tr>
<td>Rotatory</td>
<td>Combinations: MCL checks external rotation; ACL checks internal rotation</td>
</tr>
</tbody>
</table>

>iT, iliobial.

• Instant center of rotation within the talus
• Lateral and posterior points at the tips of the malleoli
• Change slightly with movement
• Talus described as a cone
• Body and trochea wider anteriorly and laterally
• Therefore talus and fibula externally rotate slightly with dorsiflexion
• Dorsiflexion and abduction are coupled.
• ROM
  • Dorsiflexion: 25 degrees
  • Planter flexion: 35 degrees
  • Rotation: 5 degrees

### Kinetics

- Tibiotalar articulation
- Major weight-bearing surface of the ankle
- Supports compressive forces up to five times body weight (W)
- Shear (backward to forward) forces are decreased by muscle activation/contraction
- Large weight-bearing surface area decreases joint stress
- Fibular/talar joint transmits about one sixth of the force
• Highest net muscle moment occurs during terminal-stance phase of gait.

• Other considerations
  • Stability based on articulation shape (mortise maintained by talar shape) and ligament support
  • Stability is greatest in dorsiflexion.
  • During weight bearing, tibial and talar articular surfaces contribute most to stability.
  • Windlass action
  • Full dorsiflexion is limited by the plantar aponeurosis.
  • Further tension on the aponeurosis (toe dorsiflexion) raises the arch.
  • A syndesmosis screw limits external rotation.
  • Arthrodesis (see Fig. 1.63): neutral dorsiflexion, 5–10 degrees of external rotation, 5 degrees of hindfoot valgus angulation
  • Surgeon should anticipate 70% loss of sagittal plane motion of the foot.

• Subtalar joint (talus-calcaneus-navicular)
  • Axis of rotation
    • In the sagittal plane: 42 degrees
    • In the transverse plane: 16 degrees
  • Functions like an oblique hinge
    • Pronation coupled with dorsiflexion, abduction, and eversion
    • Supination coupled with plantar flexion, adduction, and inversion
  • ROM
    • Pronation: 5 degrees
    • Supination: 20 degrees
    • Functional ROM: approximately 6 degrees
  • Transverse tarsal joint (talus-navicular, calcaneocuboid)
    • Motion based on foot position
      • Two axes of rotation: talonavicular and calcaneocuboid
    • Eversion (early stance)
      • The joint axes are parallel.
      • ROM is allowed.
    • Inversion (late stance)
      • External rotation of the lower extremity causes the joint axes to intersect.

• Foot
  • Transmits 1.2 times body weight with walking
  • Three times body weight with running
  • Has three arches (Table 1.46)
    • Second metatarsal (Lisfranc) joint is “keylike.”
    • Stabilizes second metatarsal
    • Allows it to carry the most load with gait
    • First metatarsal bears the most load during standing
  • Expected life of Plastazote shoe insert in active adults is less than 1 month.
  • Fatigues rapidly in compression and shear
  • Should be replaced frequently or supported with other materials such as Spenco or PPT foam

<table>
<thead>
<tr>
<th>Table 1.46</th>
<th>Arches of the Foot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARCH</strong></td>
<td><strong>SKELETAL COMPONENTS</strong></td>
</tr>
<tr>
<td>Medial longitudinal</td>
<td>Calcaneus, talus, navicular, three cuneiform bones, first to third metatarsals</td>
</tr>
<tr>
<td>Lateral longitudinal</td>
<td>Calcaneus, cuboid, fourth and fifth metatarsals</td>
</tr>
<tr>
<td>Transverse</td>
<td>Three cuneiform bones, cuboid, metatarsal bases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1.47</th>
<th>Range of Motion of Spinal Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEVEL</strong></td>
<td><strong>FLEXION/EXTENSION (DEGREES)</strong></td>
</tr>
<tr>
<td>Occiput–C1</td>
<td>13</td>
</tr>
<tr>
<td>C1–C2</td>
<td>10</td>
</tr>
<tr>
<td>C2–C7</td>
<td>10–15</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>5</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>15–20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spine biomechanics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinematics</td>
</tr>
<tr>
<td>ROM by anatomic segment (Table 1.47)</td>
</tr>
<tr>
<td>Analysis based on the functional unit</td>
</tr>
<tr>
<td>Motion segment: two vertebrae and the intervening soft tissues</td>
</tr>
<tr>
<td>Six degrees of freedom exist about all three axes.</td>
</tr>
<tr>
<td>Coupled motion</td>
</tr>
<tr>
<td>Simultaneous rotation, lateral bending, and flexion or extension</td>
</tr>
<tr>
<td>Especially axial rotation with lateral bending</td>
</tr>
<tr>
<td>Instant center of rotation within the disc</td>
</tr>
<tr>
<td>Normal sagittal alignment of the lumbar spine: 55–60 degrees of lordosis</td>
</tr>
<tr>
<td>The lordosis exists because of the disc spaces (not the vertebrae).</td>
</tr>
<tr>
<td>Most lordosis occurs between L4 and S1.</td>
</tr>
<tr>
<td>Loss of disc space height can cause loss of normal lumbar lordosis.</td>
</tr>
<tr>
<td>Iatrogenic flat back syndrome of the lumbar spine</td>
</tr>
<tr>
<td>Result of a distraction force</td>
</tr>
<tr>
<td>Supporting structures</td>
</tr>
<tr>
<td>Anterior supporting structures</td>
</tr>
<tr>
<td>Anterior longitudinal ligament</td>
</tr>
<tr>
<td>Posterior longitudinal ligament</td>
</tr>
<tr>
<td>Vertebral disc</td>
</tr>
<tr>
<td>Posterior supporting structures</td>
</tr>
<tr>
<td>Intertransverse ligaments</td>
</tr>
</tbody>
</table>
- Capsular ligaments and facets
- Ligamentum flavum (yellow ligament)
- Halo vest—most effective device for controlling cervical motion
- Because of pin purchase in the skull
- Apophyseal joints
- Resist torsion during axial loading
- Attached capsular ligaments resist flexion.
- Guide the motion segment
- Direction of motion determined by orientation of the facets of the apophyseal joint
- Varies with each level
- Cervical spine facets
- Orientation: 45 degrees to the transverse plane
- Parallel to the frontal plane
- Thoracic spine facets
- Orientation: 60 degrees to the transverse plane
- Also 20 degrees to the frontal plane
- Lumbar spine facets
- Orientation: 90 degrees to the transverse plane
- Also 45 degrees to the frontal plane
- They progressively tilt up (transverse) and inward (frontal).
- Cervical facetectomy of more than 50% causes loss of stability in flexion and torsion.
- Torsional load resistance in the lumbar spine
- Facets contribute 40%
- Disc contributes 40%
- Ligamentous structures contribute 20%

**Kinetics**

- **Disc**
  - Behaves viscoelastically
  - Demonstrates creep
  - Deforms with time
  - Demonstrates hysteresis
  - Absorbs energy with repeated axial loads
  - Later decreases in function
- Compressive stresses highest in the nucleus pulposus
- Tensile stresses highest in the annulus fibrosus
- Stiffness increases with compressive load.
- Higher loads increase deformation and creep rate.
- Repeated torsional loading (shear forces)
  - Such repeated loading may separate the nucleus pulposus from the annulus and end plate.
  - Nuclear material may then be forced through an annular tear.
- Loads increase with bending and torsional stresses.
- After subtotal discectomy, extension is the most stable loading mode.
- Disc pressures are lowest with lying supine, higher with standing, and highest with sitting.
- Carrying loads
  - Disc pressures are lowest when the load is close to the body.
- **Vertebrae**
  - Strength is related to bone mineral content and vertebrae size.
  - Increased in lumbar spine
  - Fatigue loading may lead to pars fractures.
  - Compression fractures occur at the end plate.

### Table 1.48 Shoulder Biomechanics: Muscle Forces

<table>
<thead>
<tr>
<th>MOTION</th>
<th>MUSCLE FORCES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLENOHUMERAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abduction</td>
<td>Deltoid, supraspinatus</td>
<td>Cuff depresses head</td>
</tr>
<tr>
<td>Adduction</td>
<td>Latissimus dorsi</td>
<td></td>
</tr>
<tr>
<td>Forward flexion</td>
<td>Pectoralis major, deltoid (anterior), biceps</td>
<td></td>
</tr>
<tr>
<td>Extension</td>
<td>Latissimus dorsi</td>
<td></td>
</tr>
<tr>
<td>Internal rotation</td>
<td>Subscapularis, teres major</td>
<td></td>
</tr>
<tr>
<td>External rotation</td>
<td>Infraspinatus, teres minor, deltoid (posterior)</td>
<td></td>
</tr>
<tr>
<td><strong>SCAPULAR</strong></td>
<td></td>
<td>Works through a force couple</td>
</tr>
<tr>
<td>Rotation</td>
<td>Upper trapezius, levator scapulae (anterior), serratus anterior, lower trapezius</td>
<td></td>
</tr>
<tr>
<td>Adduction</td>
<td>Trapezius, rhomboid, latissimus dorsi</td>
<td></td>
</tr>
<tr>
<td>Abduction</td>
<td>Serratus anterior, pectoralis minor</td>
<td></td>
</tr>
</tbody>
</table>

**Vertebral body stiffness is decreased in osteoporosis.**

- Caused by loss of horizontal trabeculae
- Spinal arthrodesis is helpful
- Increasing implant stiffness
- Increases probability of successful fusion
- Increases likelihood of decreased bone mineral content of the bridged vertebrae

**Sholder biomechanics (Table 1.48)**

- **Kinematics**
  - Scapular plane
    - Positioned 30 degrees anterior to the coronal plane
    - The preferred reference plane for ROM
    - Abduction requires external rotation of the humerus.
    - To prevent greater tuberosity impingement
    - With internal rotation contractures, abduction limited to 120 degrees
  - Abduction
    - Glenohumeral motion: 120 degrees
    - Scapulothoracic motion: 60 degrees
    - In ratio of 2:1
    - Varies over the first 30 degrees of motion
  - Scapulothoracic motion
    - Acromioclavicular joint movement during the early part
    - Sternoclavicular movement during the later portion
    - With clavicular rotation along the long axis
    - Surface joint motion in the glenohumeral joint is a combination of rotation, rolling, and translation.

- **Kinetics**
  - Zero position
    - Abduction of 165 degrees in the scapular plane
    - Minimal deforming forces about the shoulder
    - Ideal position for reducing shoulder dislocations
    - Also for reducing “fractures with traction”
  - Abduction
    - Glenohumeral motion: 120 degrees
    - Scapulothoracic motion: 60 degrees
  - In ratio of 2:1
  - Varies over the first 30 degrees of motion

- **Stability**
  - Limited about the glenohumeral joint
  - Humeral head surface area larger than glenoid area:
    - $48 \times 45$ mm versus $35 \times 25$ mm
  - Bony stability is limited
• Relies on humeral head inclination (125 degrees) and retroversion (25 degrees)
• Also relies on slight glenoid retrotilt
  **Inferior glenohumeral ligament (anterior band)**
  • The most important static stabilizer
  • Superior and middle glenohumeral ligaments: secondary stabilizers to anterior humeral translation
• Inferior subluxation prevented by negative intraarticular pressure
• Rotator cuff muscles
  • Dynamic contribution to stability
• Arthrodesis (see Fig. 1.63): 15–20 degrees of abduction, 20–25 degrees of forward flexion, 40–50 degrees of internal rotation
  • Excessive external rotation should be avoided
• Other joints
  • Acromioclavicular joint
  • Scapular rotation through the conoid and trapezoid ligaments
  • Scapular motion through the joint itself
  • Sternoclavicular joint
  • Clavicular protraction/retraction in a transverse plane through the coracoclavicular ligament
  • Clavicular elevation and depression in the frontal plane
  • Also through the coracoclavicular ligament
  • Clavicular rotation around the longitudinal axis

**Elbow biomechanics**
• Functions
  • A component joint of the lever arm when the hand is positioned
  • Fulcrum for the forearm lever
  • Weight-bearing joint in patients using crutches
  • Activities of daily living
• Kinematics
  • Flexion and extension
    • 0–150 degrees
    • Functional ROM: 30 to 130 degrees
    • Axis of rotation: the center of the trochlea
  • Pronation and supination
    • Pronation: 80 degrees
    • Supination: 85 degrees
    • Functional pronation and supination: 50 degrees each
    • Axis: capitellum through radial head to ulnar head (forms a cone)
  • Carrying angle
    • Valgus angle at the elbow
    • For boys and men: 7 degrees; for girls and women: 13 degrees
    • Decreases with flexion
• Kinetics
  • Flexion is accomplished primarily by the brachialis and biceps.
  • Extension is accomplished by the triceps.
  • Pronation is accomplished by pronators (teres and quadratus).
  • Supination is accomplished by the biceps and supinator.
  • Static loads approach, and dynamic loads exceed, body weight.
  • Stability

**Table 1.49 Columns of the Wrist**

<table>
<thead>
<tr>
<th>COLUMN</th>
<th>FUNCTION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>Flexion-extension</td>
<td>Distal carpal row and lunate (link)</td>
</tr>
<tr>
<td>Medial</td>
<td>Rotation</td>
<td>Mobile</td>
</tr>
<tr>
<td>Lateral</td>
<td></td>
<td>Triquetrum Scaphoid</td>
</tr>
</tbody>
</table>

• Provided partially by articular congruity
• Three necessary and sufficient constraints for stability
  • Coronoid
  • Lateral (ulnar) collateral ligament (LCL)
  • Anterior band of the MCL
    • Most important: anterior oblique fibers
    • Stabilizes against both valgus angulation and distractional force at 90 degrees
  • Most important secondary stabilizer against valgus stress: radial head
    • About 30% of valgus stability
    • Important at 0 to 30 degrees of flexion and pronation
  • In extension, capsule is the primary restraint to distractional forces.
  • Lateral stability is provided by LCL, anconeus, and joint capsule.
• Unilateral arthrodesis (see Fig. 1.63): 90 degrees of flexion
• Bilateral arthrodesis (see Fig. 1.63)
  • One elbow at 110 degrees of flexion for the hand to reach the mouth
  • Other at 65 degrees of flexion for perineal hygiene
  • Arthrodesis is difficult to perform and (fortunately) rarely required.
• Forearm
  • Ulna transmits 17% of the axial load
  • Line of the center of rotation runs from radial head to distal ulna

**Wrist and hand biomechanics**
• Wrist
  • Part of an intercalated link system
• Kinematics
  • Normal ROM
    • Flexion: 65 degrees
      • Functional: 10 degrees
    • Extension: 55 degrees
      • Functional: 35 degrees
    • Radial deviation: 15 degrees
      • Functional: 10 degrees
    • Ulnar deviation: 35 degrees
      • Functional: 15 degrees
  • Flexion and extension
    • Two-thirds radiocarpal
    • One-third intercarpal
  • Radial deviation
    • Primarily intercarpal movement
  • Ulnar deviation
    • Relies on radiocarpal and intercarpal motion
    • Instant center is usually the head of the capitate, but it varies.
• Columns of the wrist are listed in Table 1.49.
• Link system
  • A system of three links in a “chain”
• Radius, lunate, and capitate
• Less motion is required at each link.
• However, it adds to instability of the chain.
• Stability is enhanced by strong volar ligaments.
• Also by the scaphoid, which bridges both carpal rows

• Relationships
  • Carpal collapse
    • Ratio of carpal height to third MC height: normally 0.54
  • Ulnar translation
    • Ratio of ulna-to-capitate length to third MC height
    • Normal is 0.30
  • Distal radius normally bears about 80% of distal radioulnar joint load.
  • Distal ulna bears 20%
    • Ulnar load bearing increases with ulnar lengthening and decreases with ulnar shortening.
  • Wrist arthrodesis is relatively common.
    • Dorsiflexion of 10–20 degrees is good for unilateral fusion (see Fig. 1.63).

• Bilateral fusion
  • Avoided if possible
  • If necessary, other wrist should be fused at 0–10 degrees of palmar flexion.

• Hand
  • Kinematics
    • ROM
      • Metacarpophalangeal (MCP) joint
        • Universal joint, 2 degrees of freedom
        • Flexion: 100 degrees
        • Abduction-adduction: 60 degrees
      • Proximal interphalangeal (PIP) joints
        • Flexion: 110 degrees
      • DIP joints
        • Flexion: 80 degrees
  • Arches
    • Two transverse arches
      • Proximal through carpus
      • Distal through metacarpal heads
    • Five longitudinal arches
      • Through each of the rays
  • Stability
    • MCP joint
      • Volar plate and the collateral ligaments
      • Collateral ligaments: taut in flexion, lax in extension
    • PIP and DIP joints
      • Rely more on joint congruity
      • Ratio of ligament surface to articular surface is large.
  • Other concepts

Table 1.50  Recommended Positions of Flexion for Arthrodesis of the Joints of the Hand

<table>
<thead>
<tr>
<th>JOINT</th>
<th>DEGREES OF FLEXION</th>
<th>OTHER FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP</td>
<td>20–30</td>
<td>Less radial than ulnar</td>
</tr>
<tr>
<td>PIP</td>
<td>40–50</td>
<td></td>
</tr>
<tr>
<td>DIP</td>
<td>15–20</td>
<td>MC in opposition</td>
</tr>
<tr>
<td>Thumb CMC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thumb MCP</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Thumb IP</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

• Hand pulleys prevent bowstringing and decrease tendon excursion.
• Bowstringing increases moment arms.
• Sagittal bands allow MCP extension.
• With hyperextension of the MCP, the intrinsic muscles must function to produce PIP extension, because the extension tendon is lax.
• Normal grasp
  • For boys and men: 50 kg
  • For girls and women: 25 kg
  • Only 4 kg needed for daily function
• Normal pinch
  • For boys and men: 8 kg
  • For girls and women: 4 kg
  • Only 1 kg needed for daily activities

• Kinetics
  • Joint loading with pinch mostly in MCP
    • Because MCP joints have large surface area, however, contact pressures (joint load/contact area) are lower.
  • DIP joints have the most contact pressure.
    • Subsequently develop the most degenerative changes with time (Heberden nodes)
  • Grasping contact pressures are decreased, focused on MCP.
    • Patients with MCP arthritis often had occupations in which grasping was required.
  • Compressive loads occur at the thumb with pinching.
    • At interphalangeal joint: 3 kg
    • At MCP joint: 5 kg
    • At carpometacarpal (CMC) joint: 12 kg
    • An unstable joint
    • Frequently leads to degeneration
  • Recommended positions for arthrodesis of the hand are summarized in Table 1.50.

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The selected bibliography for this chapter can be found on https://expertconsult.inkling.com.
SECTION 1 ORTHOPAEDIC TISSUES

I. Bone

- Haversian canals carry nerves and blood vessels longitudinally in bone, and Volkmann canals connect different haversian canals.
- Cellular biology:
  - Osteoblasts are derived from undifferentiated mesenchymal stem cells, and RUNX2 is the multifunctional transcription factor that directs this process.
  - Wnt/Beta-catenin (B-catenin) pathways are involved in osteoblast differentiation.
  - Sclerostin and Dkk-1 inhibit binding of the Wnt molecule to LRP5/6.
  - BMPs work through SMAD to cause osteoblastic differentiation.
  - Osteoblasts produce type I collagen (i.e., bone), alkaline phosphatase, osteocalcin, bone sialoprotein, and RANKL.
  - Osteocytes are former osteoblasts surrounded by newly formed matrix. They are important for control of extracellular calcium and phosphorous concentration, and are less active in matrix production than are osteoblasts.
  - Osteoclasts are derived from hematopoietic cells in the macrophage lineage. RANKL is produced by osteoblasts, binds to immature osteoclasts, and stimulates differentiation into active, mature osteoclasts that result in an increase in bone resorption. OPG inhibits bone resorption by binding and inactivating RANKL.
  - Denosumab is a monoclonal antibody that targets and inhibits binding of RANKL to the RANK receptor, which is found on osteoclasts.
  - Osteoclasts bind to bone surfaces by means of integrins (vitronec tin receptor), effectively sealing the space below, and then create a ruffled border and remove bone matrix by proteolytic digestion through the lysosomal enzyme cathepsin K.
  - Bisphosphonates directly inhibit osteoclastic bone resorption. Nitrogen-containing bisphosphonates are up to 1000-fold more potent than non-nitrogen-containing bisphosphonates. Bisphosphonates function by inhibiting farnesyl pyrophosphate synthase in the mevalonate pathway. They are associated with osteonecrosis of the jaw, and in animal models, they have reduced the rate of spinal fusion.
  - Bone matrix is 60% inorganic (mineral) components and 40% organic components. Calcium hydroxyapatite $\text{Ca}_n\text{(PO}_4\text{)}_m\text{(OH)}_2$ constitutes the majority of the inorganic matrix. Type I collagen is 90% of the organic component, and osteocalcin is the most abundant noncollagenous protein in bone.
  - Wolff’s law: Remodeling occurs in response to mechanical stress. Huetter-Volkmann law: Compressive forces inhibit growth, whereas tension stimulates it.
  - There are three major types of bone formation. In enchondral formation, bone replaces a cartilage model. Intramembranous formation occurs without a cartilage model; aggregates of undifferentiated mesenchymal differentiate into osteoblasts, which form bone. In appositional formation, osteoblasts lay down new bone on existing bone, the groove of Ranvier supplies the chondrocytes.
  - There are three stages of fracture repair: inflammation, repair, and remodeling. Fracture healing type varies with treatment method. In closed treatment, healing occurs through periosteal bridging callus and interfragmentary enchondral ossification. In compression plate treatment, primarily cortical healing occurs.
  - BMP-2 is used for acute open tibia fractures; BMP-7 is used for tibial nonunions. BMP-3 has no osteogenic activity.
  - NSAIDs adversely affect healing of fractures as well as of lumbar spinal fusions. COX-2 activity is required for normal enchondral ossification during fracture healing.
  - Bone grafts have three properties. Osteoconducting acts as a scaffold for bone growth; osteoinduction involves growth factors that stimulate bone formation; osteogenic grafts contain primitive mesenchymal cells, osteoblasts, and osteocytes.
  - Calcium phosphate–based grafts are capable of osteoconduct and osteointegration. They have the highest compressive strength of any graft material. Calcium sulfate is osteoconductive but rapidly resorbed.
  - The primary homeostatic regulators of serum calcium are PTH and 1,25(OH)$_2$D$_3$. PTH results in increased serum Ca$^{2+}$ level and decreased inorganic phosphate level.
  - Bone mass peaks between 16 and 25 years of age. Physiologic bone loss affects trabecular bone more than cortical bone.
  - Both urinary hydroxyproline and pyridinoline cross-links are elevated when there is bone resorption.
  - Serum alkaline phosphatase increases when bone formation increases.
  - The most common cause of hypercalcemia is malignancy. Initial treatment is with hydration, which causes a saline diuresis, along with loop diuretics.
  - Renal osteodystrophy is a spectrum of disorders observed in chronic renal disease. The majority of cases are caused by phosphorous retention and secondary hyperparathyroidism.
  - Rickets (in children) and osteomalacia (in adults) are caused by a failure of mineralization. In rickets, the width of the zone of provisional calcification is increased, which causes physeal widening and cupping.
  - Premature arrest following growth plate injury is attributed to vascular invasion across the physis.
  - Osteoporosis is a quantitative defect in bone. It is defined as a lumbar bone density of 2.5 or more standard deviations less than the peak bone mass of a healthy 25-year-old (T-score).
  - Loss of function of the OPG gene results in osteoporosis.
  - Treatment of osteoporosis includes calcium supplements of 1000–1500 mg/day as well as bisphosphonates.
  - Scurvy results from ascorbic acid deficiency, which causes a decrease in chondroitin sulfate synthesis and ultimately defective collagen growth and repair. Widening in the zone of provisional calcification is observed.
  - Osteogenesis imperfecta is caused primarily by a mutation in genes responsible for metabolism and synthesis of collagen type I.

II. Cartilage and Joint

- Cartilage is viscoelastic (properties vary depending on rate of force application).
  - Composed of water (75%), collagen (25% wet weight, 90%–95% is type II), and proteoglycans (10% wet weight)
  - Collagen contributes to viscoelastic behavior in that it restrains “swelling” of aggrecan.
  - Aggrecan is most common proteoglycan.
  - Increases osmotic pressure and is responsible for ECM’s hydrophilic behavior
  - Chondrocytes are only cell in cartilage.
    - BMP-2 and the transcriptional factor SOX-9 important in regulating differentiation and formation.
    - Have cilia that serve as mechanosensory organs or “antennae.”
  - Cartilage layers:
    - Zone 1 (superficial) has highest concentration of collagen and lowest of PG.
Muscle cises and may be associated with changes in I-band.

Delayed-onset muscle soreness more common after eccentric exercises and may be associated with changes in I-band.
**TESTABLE CONCEPTS**

- C-reactive protein is the most sensitive monitor of the course of infection; it has a short half-life and dissipates about 1 week after effective treatment.
- Necrotizing fasciitis is most commonly polymicrobial and associated with diabetes.
  - Requires early débridement/amputation above level of infection.
- Only 100 bacteria are required to cause infection in the presence of a foreign object; fibronectin increases adhesion, and glycolalayx-biofilm-slime-polysaccharide capsule inhibits phagocytosis.
- Three basic mechanisms of antibiotic resistance have been identified: avoidance, decreased susceptibility, and inactivation. Biofilm formation is an example of avoidance; the biofilm creates a physical barrier.
- Superantigens like TSS toxin–1 trigger cytokine release from T cells.
- Smoking leads to two to four times more infections/osteomyelitis.
- Hyperglycemia impairs wound healing and decreases ability to fight infection.
- Lyme arthritis can be treated effectively with oral antibiotics. Adults can be given amoxicillin, doxycycline, or cefuroxime for 4 weeks.
- *Clostridium tetani* produces an exotoxin leading to tetanospasms. Td vaccine is recommended every 10 years.
- Sequestrum is the dead bone nidus with surrounding granulation tissue. Involucrum is periosteal new bone formation.
- MRI is the best method to show early osteomyelitis but may overestimate extent of disease.
- *Kingella kingae* can be difficult to culture; PCR should be considered in the toddler with a septic knee.
- *Staphylococcus epidermidis* is the most common organism in implant-associated infections.
- Antibiotic therapy according to Gustilo classification of open fractures:
  - Gustilo I and II: first-generation cephalosporins the treatment of choice
  - Gustilo IIIA: first-generation cephalosporin plus an aminoglycoside
  - Gustillo IIIB (grossly contaminated): first-generation cephalosporin plus aminoglycoside plus penicillin
- Antibiotics:
  - Aminoglycosides inhibit translation through irreversible binding of the 30S ribosomal subunit, inhibiting translation of proteins.
  - Cephalosporins inhibit cell-wall production by preventing peptidoglycan cross-linkage.
  - Glycopeptides, such as vancomycin, inhibit cell-wall production by interfering with the addition of cell-wall subunits.
  - Rifamycin inhibits DNA-dependent RNA polymerase F and displays excellent biofilm penetration. Bacteria develop rapid resistance to rifampin used as monotherapy.
  - Macrolides, like erythromycin, bind the 50S ribosomal subunits.
  - Fluoroquinolones, such as ciprofloxacin, inhibit DNA gyrase.
  - Beta–lactam antibiotics, like penicillin, work by inhibiting peptidoglycan synthesis by binding to the bacterial cell membrane surface penicillin-binding proteins.

**SECTION 3 PERIOPERATIVE AND ORTHOPAEDIC MEDICINE**

**I. Thromboprophylaxis**
- Virchow triad: endothelial damage, stasis or decreased blood flow, and hypercoagulability.
- Aspirin irreversibly binds and inactivates COX enzyme in platelets, reducing thromboxane A₂.
- Warfarin can be reversed with fresh frozen plasma and vitamin K.
- Heparin and low-molecular-weight heparin act through ATIII and can be reversed by protamine sulfate.
- Rivaroxaban is a direct factor Xa inhibitor.
- Lactate is an indirect marker of tissue hyperperfusion and serves as best measure of resuscitation.

**II. Perioperative Disease and Comorbidities**
- Ratio of 1:1:1 blood product resuscitation is superior to saline fluid.
- Fat embolism syndrome classical triad = petechial rash, neurologic symptoms, respiratory decline.
- Malignant hyperthermia is autosomal dominantly inherited defect in ryanodine receptor.
  - Caused by an uncontrolled release of calcium
  - Triggered by volatile anesthetics (and succinylcholine)
  - Early sign is increasing end-tidal CO₂
  - Treatment is 100% O₂ and dantrolene (stabilizes sarcoplasmic reticulum).

**SECTION 4 OTHER BASIC PRINCIPLES**

**I. Imaging and Special Studies**
- Increased radiation exposure associated with:
  - Imaging of larger body parts
  - Positioning the extremity closer to the x-source
  - Use of large C-arm rather than mini C-arm
  - 3.0T MRI has 9 times greater proton energy than 1.5T.

**II. Biomaterials and Biomechanics**
- Work is the product of force and the displacement it causes (Joule).
- Energy is the ability to perform work.
  - Potential energy is stored
  - Kinetic energy is energy caused by motion: 1/2 mv².
- Stress is the internal resistance of body to a load (force/area).
- Strain is relative measure of deformation = change in length/original length (no units).
- Young’s modulus of elasticity (E) = stress/strain.
  - Unique for every material
  - High E to low E: ceramic, cobalt chrome, stainless steel, titanium, cortical bone, PMMA, polyethylene, cancellous bone, tendon/ligament, cartilage
- Viscoelastic materials have a stress-strain behavior that is time/rate dependent.
- Isotropic materials have mechanical properties that are the same for all directions loaded (golf ball).
- Anisotropic materials have mechanical properties that vary with the direction of the applied load (bone is stronger in axial load than with bending moment).
- Corrosion:
  - Galvanic corrosion occurs when dissimilar metals are in direct contact (cobalt chrome and stainless steel).
  - Crevice corrosion occurs in fatigue cracks with low oxygen tension.
  - Fretting corrosion comes from small movements abrading the outside layer.
- Stress corrosion occurs in areas with high stress gradients.

**Joint arthrodesis:**
- Hip: 25–30 degrees of flexion; 0 degrees of abduction/rotation
- Knee: 0–7 degrees of valgus; 10–15 degrees of flexion
- Ankle: 5 degrees of hindfoot valgus; 5–10 degrees of external rotation; neutral dorsiflexion
- Shoulder: 15–20 degrees of abduction; 20–25 of forward flexion; 40 degrees of internal rotation
- Elbow: 90 degrees of flexion if unilateral; if bilateral, one at 65 degrees and one at 110 degrees
- Wrist: 10–20 degrees of dorsiflexion; if bilateral, then the opposite should be in 10 degrees of palmarflexion.

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