Module 6.1: Introduction to Bones as Organs (Figures 6.1, 6.2, 6.3, 6.4)

A. The **skeletal system** includes the bones, joints, and their associated supporting tissues. What are the main organs of this system? __________

Like any organ, they are composed of more than just osseous tissue. Bones are also composed of both dense __________ and __________ collagenous connective tissue, as well as bone marrow.

B. Describe the Following Functions of the Skeletal System (Figure 6.1):

1. **Protection:** __________

2. **Mineral storage and acid-base homeostasis:** __________

3. **Blood cell formation:** __________

4. **Fat storage:** __________

5. **Movement:** __________

6. **Support:** __________

C. **Bone structure** can be organized into five classes, despite the diversity of bone appearance, where all 206 bones fit into one of the following categories based on their shape (Figure 6.2):
1. **Classification of bones by shape:**
   
a. **Long bones** are named for the overall shape, not their actual size. These bones are longer than they are wide. **Provide some examples of long bones:** ________________________________
   
   ________________________________ (Figure 6.2a)
   
b. **Short bones** are also named for their shape rather than their size. These bones are roughly cube-shaped, or about as long as they are wide. **Provide some examples of short bones:**
   
   ________________________________ (Figure 6.2b)
   
c. **Flat bones** are thin and broad bones. **Provide some examples of flat bones:** ________________________________
   
   ________________________________ (Figure 6.2c)
   
d. **Irregular bones** do not fit into the other classes because of their irregular shapes. **Provide some examples of irregular bones:** ________________________________
   
   ________________________________ (Figure 6.2d)
   
e. **Sesamoid bones** are specialized bones located within tendons. These are usually small, flat, and oval-shaped bones that give tendons a mechanical advantage, which gives muscle better leverage. The patella, or kneecap, is an example of this class of bones (Figure 6.2e).

2. The **structure of a long bone** includes the following features (Figure 6.3):
   
a. The___________ is a membrane composed of dense irregular collagenous connective tissue that forms a covering, rich with blood vessels and nerves, which surrounds the outer surface of long bones (Figure 6.3a).
   
b. __________________________ (or Sharpey’s fibers) are made of collagen that anchors the periosteum firmly to the underlying bone surface by penetrating deep into the bone matrix.
c. The shaft of a long bone is called its______________ while each end is called its______________. Each epiphysis is covered with a thin layer of hyaline cartilage known as ________________ because it is found within the joints between bones, otherwise known as articulations.

d. The diaphysis, or shaft, is a hollow cavity also known as the ________________ cavity, where either red or yellow bone marrow is found depending on the bone and the age of the individual (Figure 6.3b).

e. ________________ bone, one of two bone textures, is the hard, dense outer region that allows bone to resist linear compression and twisting forces among other stresses placed on long bones.

f. ________________ bone (or cancellous bone), the second bone texture found inside the cortical bone, is a honeycomb-like framework of bony struts that allows long bones to resist forces from many directions and provides a cavity for bone marrow.

g. The bony struts of spongy bone and all inner surfaces of bone are covered by a thin membrane called the______________.

h. ________________ are found separating both proximal and distal epiphyses from the diaphysis. These are the remnants of the epiphyseal plates, or growth plates, which is a line of hyaline cartilage found in the developing bones of children.

3. Structure of short, flat, irregular, and sesamoid bones: these bones do not have______________.______________.______________ cavities,______________ lines, or______________ plates (Figure 6.4).

a. These bones are covered by periosteum and their associated perforating fibers, blood vessels, and nerves, like long bones.

b. The internal structure is composed of two outer layers of thin ________________ bone with a middle layer of spongy bone,
called__________, and its associated bone marrow. Some flat and irregular bones of the skull contain hollow, air-filled spaces called sinuses, which reduces bone weight.

4. **Blood and nerve supply to bone**: bones are well supplied with blood vessels and sensory nerve fibers

5. **Red bone marrow** consists of loose connective tissue that supports islands of blood-forming hematopoietic cells.
   a. Where is red marrow found in adults? ________________

   ________________

   ________________
   b. Children need more red marrow to assist in their growth and development.

6. **Yellow bone marrow** is composed of______________, ________

   ____________, and___________.

Module 6.2: Microscopic Structure of Bone Tissue (Figures 6.5, 6.6, 6.7, 6.8, 6.9, 6.10)

A. **Bone**, or osseous tissue, the primary tissue found in bone, is composed mostly of extracellular matrix with a small population of cells scattered throughout.

B. **The extracellular matrix of bone** or bone matrix is unique. **Inorganic matrix** consisting of minerals makes up about____% of bones total weight. **Organic matrix** makes up the remaining____% consists of collagen fibers and the usual ECM components (Figure 6.5).

1. Inorganic matrix is made up predominantly of calcium salts. Bone stores around 85% of the total__________ions in the body as well as a large amount of___________.
   a. Calcium and phosphorus salts exist as large molecules of a mineral called____________________crystals [Ca_{10}(PO_4)_6(OH)_2]. This crystalline structure makes bone one of the hardest substances in the body that makes it strong and resistant to compression. This structural strength allows bone to be both protective and supportive.
b. Bicarbonate, potassium, magnesium, and sodium are also found in the inorganic matrix

2. Organic matrix is known as osteoid, which consists of protein fibers, proteoglycans, glycosaminoglycans, glycoproteins, and bone-specific proteins.
   a. What is the predominant protein fiber in bone?
      Collagen forms cross-links with one another and helps bone resist twisting and pulling or stretching forces. Collagen fibers also align themselves with hydroxyapatite crystals, which enhance the hardness of bone.
   b. Glycosaminoglycans and proteoglycans create an osmotic gradient that draws water into the osteoid, which helps the tissue resist __________.
   c. Glycoproteins in the osteoid bind all of the different components of the osteoid and the inorganic matrix.

C. Bone is a dynamic tissue that is continually changing as older bone is broken down for the raw materials to build new bone. The following three types of bone cells are responsible for bone’s dynamic nature (Figures 6.6, 6.7, 6.8):

1. Describe the function of osteoblasts. _____________________________

   _____________________________ (Figure 6.7.1)

   These metabolically active bone cells are found in the periosteum and endosteum. Osteogenic cells differentiate into osteoblasts when stimulated by specific chemical signals.

2. Describe the function of osteocytes. _____________________________

   _____________________________ (Figure 6.7.2)

   Osteocytes are no longer metabolically active except for the local need for maintaining bone extracellular matrix (Figure 6.7.3).

3. Describe the function of osteoclasts. _____________________________
These large multinucleated cells are derived from the fusion of cells from the bone marrow (Figure 6.8).

D. The **histology of bone tissue** is quite different between the hard outermost compact bone and the porous inner spongy bone. Both gross and histological differences can be attributed to the different functions each region performs (Figures 6.9, 6.10).

1. The **structure of compact bone** is continuously subjected to a great deal of _________. Stress tends to strain or deform objects like bone so it must be able to withstand these forces or suffer damage (Figure 6.9).

2. Compact bone, in cross-section, is organized into a unit called an ________, or a Haversian system. The **osteon structure** consists of the following components:
   a. Each osteon contains__________ arranged in layered ring structures. This strong lamellar arrangement is very stress resistant. In addition, collagen fibers of neighboring lamellae run in opposite directions, which resist twisting and bending forces placed on bone from a variety of directions.
   b. The__________ is an endosteum-lined hole found in the center of each osteon where blood vessels and nerves reside to supply the bone.
   c. Osteocytes reside in__________, which are the small cavities found between lamellae that are filled with extracellular fluid.
   d. Neighboring lacunae are connected to one another by a network of small passageways, or canals in the bone matrix, called __________. The cytoplasmic extensions of osteocytes extend through these networks allowing neighboring cells to share resources and to communicate with one another.

3. **Overall Compact Bone Structure.** Osteons are not permanent structures as osteoclasts breakdown and osteoblasts rebuild bone matrix depending on the
needs of the bone or the body. This process leaves behind the following characteristic features in compact bone.

a. _____________ lamellae __ are found filling the spaces between circular osteons and represent the remnants of old osteons.

b. _____________ lamellae __ are the outer and inner layers of lamellae just inside the periosteum and at the boundary with spongy bone. These add strength to the bone.

c. _____________ canals, __ or Volkmanns’ canals, originate from the blood vessels in the periosteum and travel in right angles or perpendicular to the central canals of neighboring osteons and serve to connect them with one another.

4. **Structure of spongy bone:** Spongy bone is usually not weight-bearing like compact bone so is much less densely packed. Spongy bone is a network of struts that reinforce the strength of compact bone by resisting forces from a variety of directions as well as providing a protective structure for bone marrow tissue (Figure 6.10).

a. The struts, or ribs, of bone are called___________, which are covered with endosteum and are usually not arranged into osteons. Trabeculae are composed of___________ lamellae between which lacunae are found containing osteocytes that communicate with each other through canaliculi.

b. **Since there are no central or perforating canals supplying blood to the trabeculae, how do trabeculae obtain their blood supply?**

________________________________________________________________________

**Module 6.3: Bone Formation: Ossification (Figures 6.11, 6.12)**

A. The process of bone formation is called___________, or osteogenesis. It begins in the embryonic period and continues through childhood with most bones completing the process by age seven.

1. Ossification can proceed by two different mechanisms but both have similar features including:
a. The first bone formed is immature primary, or woven bone, consisting of irregularly arranged collagen bundles, osteocytes, and sparse inorganic matrix.

b. Usually \underline{primary} bone is broken down by osteoclasts and replaced with mature \underline{bone}, which has more inorganic matrix and increased strength.

2. The bones formed by \underline{ossification} are built on a model or a starting material made of a membrane of embryonic connective tissue.

3. The bones formed by \underline{ossification} are built on a model of hyaline cartilage.

B. **Intramembranous ossification** is the process that forms many \underline{bones}, including the bones of the skull and the clavicles during fetal development. (Figure 6.11).

1. Primary bone is formed within a mesenchymal membrane composed of embryonic connective tissue, which is richly supplied with blood and populated with mesenchymal cells.

2. Recall that flat bone structure essentially is two outer layers of compact bone with an inner or middle layer of spongy bone.

3. The middle layer of spongy bone ossifies before the outer compact bone layers and begins from a region called the \underline{ossification center}.

4. Intramembranous ossification begins with at the primary ossification center and proceeds through the following steps (Figure 6.11):
   a. Mesenchymal cells differentiate into \underline{cells} then \underline{at the primary ossification site}.

   b. Osteoblasts secrete the \underline{calcium salts and other inorganic matrix components} are deposited in the trabeculae over a few days, a process called \underline{which hardens the primary bone}. Osteoblasts get trapped in \underline{and become \underline{}}.
c. Early spongy bone is formed as____________ continue to lay down new bone to form trabeculae. Smaller trabeculae can merge forming larger structures.

d. Some mesenchymal cells differentiate and form the periosteum while some of the vascular tissue in the early spongy bone will become bone marrow.

e. Early compact bone is formed as the_________bone deep to the periosteum becomes heavily calcified and its structure is rearranged to form immature compact bone.

5. Larger bones have more than one___________ ossification center which leads to pieces of bone that must fuse to one another over time. An example of early incomplete ossification is the fontanelles, or soft spots, in the skull of newborn babies.

C. **Endochondral ossification** is the method of bone development for all the bones below the head except the clavicles. This process begins in the fetal stage of development of most bones although some bones ossify much later (**Figure 6.12**).

1. Endochondral ossification occurs from within a model of ___________ cartilage, which serves as a scaffold for the developing bone.
   
   a. The hyaline cartilage model is composed of chondrocytes, collagen, and ECM, all surrounded by a connective tissue membrane called the ________________ and immature cartilage cells called ________________.

   b. This process also begins at a_____________ ossification center where_____________ bone is first synthesized and then replaced with_____________ bone.

   c. Long bones have______________ ossification centers found in their epiphyses that ossify by a similar pattern.

2. Once the cartilage model is completed, the sequence of events that characterize endochondral ossification occur are as follows (**Figure 6.12**):
a. Chondroblasts in the perichondrium differentiate first into
_____________ then _______________ and the
_____________ has formed.

b. Bone begins to form from the outside where osteoblasts have built a
_____________ on the external surface of bone.

c. At the same time the bone collar forms, internal cartilage begins to
___________ and chondrocytes die off as their connection to the blood
supply is severed. Calcified cartilage and tiny cavities are left behind.

d. In the__________ ossification center, osteoblasts replace the
calcified cartilage with early ________ bone. The ________
ossification centers and the__________cavity begin development.

e. As the medullary cavity enlarges, the remaining cartilage is replaced
by bone, and the epiphyses finish ossifying.

f. Calcified cartilage is replaced with and the medullary cavity is
filled with ________________.

g. Cartilage only persists in two places: the_________________ and
the_________________ where bones interact at a joint, which is
also called articular cartilage.

h. ____________ cartilage persists into adulthood while the
epiphyseal plates eventually are filled in once the bone is finished
growing in length.

Module 6.4: Bone Growth in Length and Width (Figures 6.13, 6.14)

A. Growth in Length: Long bones lengthen by a process called longitudinal
growth, which involves the division chondrocytes, not osteocytes or osteoblasts,
in the epiphyseal __________. Bone growth takes place at the epiphysis on the
side closest to the diaphysis (Figure 6.13).

1. The epiphyseal plate, composed of ____________ cartilage that did not
ossify by endochondral ossification, contains five different zones of cells,
each with a distinctive appearance.
2. Each zone of epiphyseal plate, except the zone of reserve cartilage, is actively involved in longitudinal growth. The process of longitudinal growth proceeds in the following sequence of events (Figure 6.14):
   a. Chondrocytes divide in the zone of forcing cells ahead of them into the next zones, moving toward the diaphysis.
   b. Chondrocytes that reach the zones of and enlarge and stop dividing.
   c. Chondrocytes that reach the zone of die and their matrix calcifies.
   d. Calcified cartilage is replaced with bone in the zone of where osteoblasts invade calcified cartilage and begin to lay down bone.
   e. Eventually the calcified cartilage and primary bone is resorbed by osteoclasts and completely replaced with mature bone.

3. Longitudinal growth continues at the epiphyseal plate as long as mitosis continues in the zone of .
   a. The mitosis rate slows around the ages of 12–15 years old while ossification continues which causes the epiphyseal plates to shrink as zone of proliferation is overtaken by the zone of and .
   b. Between the ages of 18–21 the zone of proliferation is completely ossified, longitudinal growth stops, and the epiphyseal plate is considered closed.
   c. The epiphyseal is a calcified remnant of the epiphyseal plate.

B. Growth in Width: bones not only grow in length they also grow in width, a process called growth.

1. , found in between the periosteum and the bone surface, lay down new bone.

2. Appositional growth does not result in the immediate formation of osteons; instead, new lamellae are formed.
3. As new lamellae are added older deeper circumferential lamellae are either removed or restructured into osteons.

4. Bones may continue to increase in width even after the epiphyseal plates have closed and the bone is no longer lengthening.

C. **Role of Hormones in Bone Growth**: multiple factors play a role in how much cell division occurs in the epiphyseal plate and how long the process remains active. One of the main factors affecting bone growth is a group of chemicals called \_

1. Hormones are secreted by the cells of the endocrine glands. \_
   hormone, secreted by the anterior pituitary gland, enhances protein synthesis and cell division in nearly all tissues, including bone tissue.

2. **Describe the effects of growth hormone on both longitudinal and appositional growth**:
   a. 
   b. 
   c. 

3. **Describe the effects of the male sex hormone testosterone on bone growth**:
   a. 
   b. 
   c. Testosterone accelerates the closure of the epiphyseal plate

4. **Describe the effects of the female sex hormone estrogen on bone growth**:
   a. 
   b. 

Module 6.5: Bone Remodeling and Repair (Figures 6.15, 6.16, 6.17; Table 6.1)

A. Once bone has finished growing in length it is far from inactive. Bone undergoes a continuous process of formation and loss called bone remodeling where new bone is formed by bone_________ and old bone is removed by bone_________. This cycle of bone formation and loss occurs to maintain calcium ion homeostasis, to replace_________ bone with _________ bone, for bone repair, for the replacement of old brittle bone with newer bone, and for adaptation to tension and stress.

B. Bone remodeling involves_________ and_________. In healthy bone the process of formation and loss occur simultaneously with bone breakdown by osteoclasts matching bone formation by osteoblasts (Figure 6.15, 6.16).

1. Process of bone remodeling involves bone deposition and bone resorption. In childhood bone_________ proceeds at a much faster rate than bone_________. Once epiphyseal plates close and longitudinal growth is complete, deposition and resorption become roughly equivalent.
   a. Bone deposition is carried out by_________, found in both the __________ and __________, which make organic matrix and facilitate the formation of the inorganic matrix.
   b. During bone resorption_________ secrete hydrogen ions on the bone ECM. Hydroxyapatite crystals in the inorganic matrix are pH-sensitive and breakdown in the acidic environment. Calcium ions and other liberated minerals can be reused elsewhere in the body.
   c. Osteoclasts secrete enzymes that degrade the organic matrix. The breakdown products are taken up into osteoclast for recycling.

2. Bone Remodeling in Response to Tension and Stress: the heavier the load or compression a bone must carry, the more bone tissue is deposited in that bone. Tension and pressure are other factors that affect remodeling.
a. What is compression? __________________________

How do bones respond to continuous compression? _________

b. Tension is a stretching force while pressure is a continuous downward force. How do bones respond to continuous pressure? _________

How do bones respond to continuous tension? _________

3. Other Factors Influencing Bone Remodeling. The following factors influence bone remodeling:
   a. Hormones: Testosterone promotes bone __________ while estrogen inhibits osteoclast activity.
   b. Age: As individuals age growth hormone and sex hormones decline which decreases __________ synthesis in bone.
   c. Calcium ion intake from the diet must be adequate to support bone deposition.
   d. Vitamins ______, _______, and ____ intake.
   e. Protein intake from the diet must be adequate for osteoblasts to synthesize the collagen fibers found in the organic matrix.

4. Bone Remodeling and Calcium Ion Homeostasis. Bone stores most of the calcium ions in the body. Stored calcium ions are not only used for bone deposition and remodeling; they are used throughout the body for several critical processes such as muscle contraction. Calcium ion levels in the blood are closely monitored. Both high and low levels of calcium ions can lead to major disruptions in homeostasis and even death. The following describes a negative feedback loop for maintaining calcium ion homeostasis in the blood (Figure 6.15).
   a. Stimulus and receptor: When calcium ion levels drops in the blood it is detected by __________ cells.
b. Control center: ____________ cells act as the control center and secrete ________________ (PTH).

c. What is the effect or response of PTH to restore blood calcium levels? 

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

d. Homeostasis and negative feedback: As calcium ion levels return to normal in the blood this change is detected by the parathyroid cells and they reduce the secretion of PTH, closing the negative feedback loop.

e. An increase in blood calcium levels triggers a different negative feedback loop, as follows.

f. Stimulus and receptor: ____________ is secreted by the thyroid gland and has basically the opposite effects as PTH.

g. What is the effect or response of calcitonin to restore blood calcium levels? Ultimately calcitonin leads to bone ____________, which pulls calcium ions out of the blood to manufacture inorganic bone matrix. Calcitonin is most active during bone growth and less so in adulthood.

h. Vitamin ____ is important for calcium ion homeostasis due to its effects on the absorption of calcium ions from the gut.

i. The factors influencing bone remodeling are summarized in Figure 6.16.

C. Bone Repair. Bones are commonly injured while performing their protective and supportive functions (Figure 6.17; Table 6.1):

1. The most dramatic bone injury is a fracture, commonly called a broken bone. These bone injuries are grouped into many different classes. The following is a basic classification of fractures (Table 6.1):

a. What is a simple fracture? ________________________________
b. **What is a compound fracture?** 

2. The general process of fracture healing involves the following steps (Figure 6.17):

   a. A hematoma fills in the gap between bone fragments. What is a hematoma? 

   b. Fibroblasts and chondroblasts infiltrate the hematoma and form a soft callus. What is a soft callus? 

   c. Osteoblasts build a bone callus. What is a bone callus? 

   d. The bone callus is remodeled and primary bone is replaced with secondary bone.