Bone:

Bone is a specialized connective tissue composed of intercellular calcified material, the **bone matrix,** and three cell types: **osteocytes**, which are found in cavities (**lacunae**) within the matrix; **osteoblasts**, which synthesize the organic components of the matrix; and **osteoclasts**, which are multinucleated giant cells involved in the resorption and remodeling of bone tissue.

Because metabolites are unable to diffuse through the calcified matrix of bone, the exchanges between osteocytes and blood capillaries depend on communication through the **canaliculi**, which are thin, cylindrical spaces that perforate the matrix.

All bones are lined on both internal and external surfaces by layers of tissue containing osteogenic cells **endosteum** on the internal surface and **periosteum** on the external surface.

Bone Cells

Osteoblasts

Osteoblasts are responsible for the synthesis of the organic components of bone matrix (type I collagen, proteoglycans, and glycoproteins). Deposition of the inorganic components of bone also depends on the presence of viable osteoblasts. Osteoblasts are exclusively located at the surfaces of bone tissue, side by side, in a way that resembles simple epithelium. When they are actively engaged in matrix synthesis, osteoblasts have a cuboidal to columnar shape and basophilic cytoplasm. When their synthesizing activity declines, they flatten, and cytoplasmic basophilia declines.

Some osteoblasts are gradually surrounded by newly formed matrix and become **osteocytes.** During this process a space called a **lacuna** is formed. Lacunae are occupied by osteocytes and their extensions, along with a small amount of extracellular noncalcified matrix.

Osteocytes

Osteocytes, which derive from osteoblasts, lie in the lacunae situated between lamellae of matrix. Only one osteocyte is found in each lacuna. The thin, cylindrical matrix canaliculi house cytoplasmic processes of osteocytes. Processes of adjacent cells make contact via gap junctions, and molecules are passed via these structures from cell to cell. Some molecular exchange between osteocytes and blood vessels also takes place through the small amount of extracellular substance located between osteocytes (and their processes) and the bone matrix. This exchange can provide nourishment for a chain of about 15 cells. Osteocytes are long-living cells.

Osteoclasts

Osteoclasts are very large, branched motile cells. Dilated portions of the cell body contain from 5 to 50 (or more) nuclei. In areas of bone undergoing resorption, osteoclasts lie within enzymatically etched depressions in the matrix known as **Howship's lacunae.** Osteoclasts are derived from the fusion of bone marrow-derived mononucleated cells.

The osteoclast secretes collagenase and other enzymes and pumps protons into a subcellular pocket (the microenvironment referred to above), promoting the localized digestion of collagen and dissolving

calcium salt crystals. Osteoclasts have receptors for calcitonin, a thyroid hormone, but not for parathyroid hormone. However, osteoblasts have receptors for parathyroid hormone and, when activated by this hormone, produce a cytokine called osteoclast stimulating factor.

Bone Matrix

Inorganic matter represents about 50% of the dry weight of bone matrix. Calcium and phosphorus are especially abundant, but bicarbonate, citrate, magnesium, potassium, and sodium are also found.

Periosteum&Endosteum

External and internal surfaces of bone are covered by layers of bone-forming **cells** and **connective tissue** called periosteum and endosteum.

The **periosteum** consists of an outer layer of collagen fibers and fibroblasts . Bundles of periosteal collagen fibers, called **Sharpey's fibers,** penetrate the bone matrix, binding the periosteum to bone. The inner, more cellular layer of the periosteum is composed of fibroblastlike cells called **osteoprogenitor cells,** with the potential to divide by mitosis and differentiate into osteoblasts. Osteoprogenitor cells play a prominent role in bone growth and repair.

The **endosteum** lines all internal cavities within the bone and is composed of a single layer of flattened osteoprogenitor cells and a very small amount of connective tissue. The endosteum is therefore considerably thinner than the periosteum.

The principal functions of periosteum and endosteum are nutrition of osseous tissue and provision of a continuous supply of new osteoblasts for repair or growth of bone.

Types of Bone

Gross observation of bone in cross section shows dense areas without cavities corresponding to **compact bone**and areas with numerous interconnecting cavities corresponding to **cancellous** (**spongy**) **bone**. Under the microscope, however, both compact bone and the trabeculae separating the cavities of cancellous bone have the same basic histological structure.

In long bones, the bulbous ends called **epiphyses** are composed of spongy bone covered by a thin layer of compact bone. The cylindrical part **diaphysis** is almost totally composed of compact bone, with a small component of spongy bone on its inner surface around the bone marrow cavity. Short bones usually have a core of spongy bone completely surrounded by compact bone. The flat bones that form the have two layers of compact bone called **plates**, separated by a layer of spongy bone**.**

Microscopic examination of bone shows two varieties: **primary, immature,** or **woven bone** and **secondary, mature,** or **lamellar bone.** Primary bone is the first bone tissue to appear in embryonic development and in fracture repair and other repair processes. It is characterized by random disposition of fine collagen fibers, in contrast to the organized lamellar disposition of collagen in secondary bone.

Primary Bone Tissue

Primary bone tissue is usually temporary and, except in a very few places in the body (eg, ***near the sutures of the flat bones*** of the skull, in ***tooth sockets***, and in the insertions of some tendons), is replaced in adults by secondary bone tissue.

Secondary Bone Tissue

Secondary bone tissue is usually found in adults. It characteristically shows collagen fibers arranged in lamellae that are parallel to each other or concentrically organized around a vascular canal. The whole complex of concentric lamellae of bone surrounding a canal containing blood vessels, nerves, and loose connective tissue is called a ***haversian system,*** *or* ***osteon***. Lacunae containing osteocytes are found between, and occasionally within, the lamellae. In each lamella, collagen fibers are parallel to each other. Surrounding each haversian system is a deposit of amorphous material called the **cementing substance** that consists of mineralized matrix with few collagen fibers.

In compact bone (eg, the diaphysis of long bones), the lamellae exhibit a typical organization consisting of ***1-haversian systems, 2-outer circumferential lamellae, 3-inner circumferential lamellae, and 4-interstitial lamellae***

Inner circumferential lamellae are located around the marrow cavity, and outer circumferential lamellae are located immediately beneath the periosteum. There are more outer than inner lamellae.

Between the two circumferential systems are numerous haversian systems, including triangular or irregularly shaped groups of parallel lamellae called **interstitial** (or **intermediate**) **lamellae.** These structures are lamellae left by haversian systems destroyed during growth and remodeling of bone.

Each haversian system is a long, often bifurcated cylinder parallel to the long axis of the diaphysis. It consists of a central canal surrounded by 4-20 concentric lamellae . Each endosteum-lined canal contains blood vessels, nerves, and loose connective tissue. The haversian canals communicate with the marrow cavity, the periosteum, and one another through transverse or oblique ***Volkmann's canals***. Volkmann's canals do not have concentric lamellae; instead, they perforate the lamellae. All vascular canals found in bone tissue come into existence when matrix is laid down around preexisting blood vessels.

Histogenesis

Bone can be formed in two ways: by direct mineralization of matrix secreted by osteoblasts (**intramembranous ossification**) or by deposition of bone matrix on a preexisting cartilage matrix (**endochondral ossification**).

Intramembranous Ossification

Intramembranous ossification, the source of most of the flat bones, is so called because it takes place within condensations of mesenchymal tissue. The frontal and parietal bones of the skull as well as parts of the occipital and temporal bones and the mandible and maxilla are formed by intramembranous ossification. This process also contributes to the growth of short bones and the thickening of long bones.

In the mesenchymal condensation layer, the starting point for ossification is called a **primary ossification center.** The process begins when groups of cells differentiate into osteoblasts. Osteoblasts produce bone matrix and calcification follows, resulting in the encapsulation of some osteoblasts, which

then become osteocytes. These islands of developing bone form walls that delineate elongated cavities containing capillaries, bone marrow cells, and undifferentiated cells. Several such groups arise almost simultaneously at the ossification center, so that the fusion of the walls gives the bone a spongy structure. The connective tissue that remains among the bone walls is penetrated by growing blood vessels and additional undifferentiated mesenchymal cells, giving rise to the bone marrow cells.

The ossification centers of a bone grow radially and finally fuse together, replacing the original connective tissue. The fontanelles of newborn infants, for example, are soft areas in the skull that correspond to parts of the connective tissue that are not yet ossified.

In cranial flat bones there is a marked predominance of bone formation over bone resorption at both the internal and external surfaces. Thus, two layers of compact bone (internal and external plates) arise, whereas the central portion maintains its spongy nature.

The portion of the connective tissue layer that does not undergo ossification gives rise to the endosteum and the periosteum of intramembranous bone.

Endochondral Ossification

Endochondral ossification takes place within a piece of hyaline cartilage whose shape resembles a small version, or model, of the bone to be formed. This type of ossification is principally responsible for the formation of short and long bones.

Endochondral ossification of a long bone consists of the following sequence of events. Initially, the first bone tissue appears as a hollow bone cylinder that surrounds the mid portion of the cartilage model. This structure, the **bone collar,** is produced by intramembranous ossification within the local perichondrium. In the next step, the local cartilage undergoes a degenerative process of programmed cell death with cell enlargement (hypertrophy) and matrix calcification, resulting in a three-dimensional structure formed by the remnants of the calcified cartilage matrix. This process begins at the central portion of the cartilage model (diaphysis), where blood vessels penetrate through the bone collar previously perforated by osteoclasts, bringing osteoprogenitor cells to this region. Next, osteoblasts adhere to the calcified cartilage matrix and produce continuous layers of primary bone that surround the cartilaginous matrix remnants. At this stage, the calcified cartilage appears basophilic, and the primary bone is eosinophilic. In this way the **primary ossification center** is produced. Then, **secondary ossification centers** appear at the swellings in the extremities of the cartilage model (epiphyses). During their expansion and remodeling, the primary and secondary ossification centers produce cavities that are gradually filled with bone marrow.

In the secondary ossification centers, cartilage remains in two regions: the **articular cartilage,** which persists throughout adult life and does not contribute to bone growth in length, and the **epiphyseal cartilage,** also called the **epiphyseal plate,** which connects the two epiphyses to the diaphysis. The epiphyseal cartilage is responsible for the growth in length of the bone, and it disappears in adults, which is why bone growth ceases in adulthood.

*Epiphyseal cartilage is divided into five zones, starting from the epiphyseal side of cartilage: (1) The**resting zone** consists of hyaline cartilage without morphological changes in the cells. (2) In the **proliferative zone,** chondrocytes divide rapidly and form columns of stacked cells parallel to the long axis of the bone. (3) The **hypertrophic cartilage zone** contains large chondrocytes whose cytoplasm has accumulated glycogen. The resorbed matrix is reduced to thin septa between the chondrocytes. (4)*

*Simultaneous with the death of chondrocytes in the **calcified cartilage zone,** the thin septa of cartilage matrix become calcified by the deposit of hydroxyapatite. (5) In the **ossification zone,** endochondral bone tissue appears. Blood capillaries and osteoprogenitor cells formed by mitosis of cells originating from the periosteum invade the cavities left by the chondrocytes. The osteoprogenitor cells form osteoblasts, which are distributed in a discontinuous layer over the septa of calcified cartilage matrix. Ultimately, the osteoblasts deposit bone matrix over the three-dimensional calcified cartilage matrix.*

In summary, growth in length of a long bone occurs by proliferation of chondrocytes in the epiphyseal plate adjacent to the epiphysis. At the same time, chondrocytes of the diaphyseal side of the plate hypertrophy; their matrix becomes calcified, and the cells die. Osteoblasts lay down a layer of primary bone on the calcified cartilage matrix. Because the rates of these two opposing events (proliferation and destruction) are approximately equal, the epiphyseal plate does not change thickness. Instead, it is displaced away from the middle of the diaphysis, resulting in growth in length of the bone.