Medical Biology

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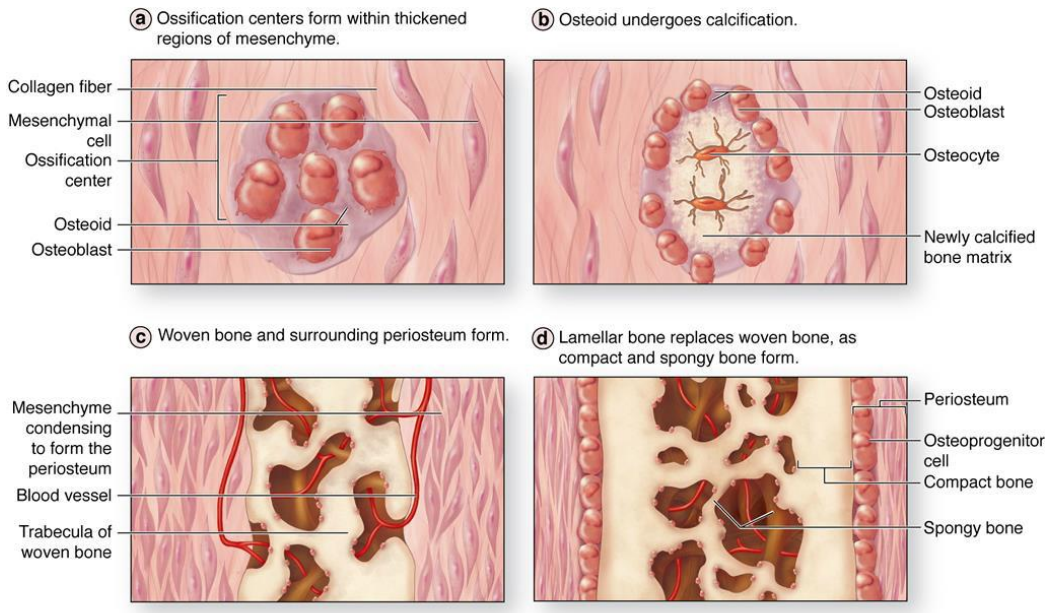
Osteogenesis

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). In both processes, the bone tissue that appears first is primary, which is soon replaced by the secondary bone.

Intramembranous Ossification:

Intramembranous ossification, the source of most of the flat bones, is so called because it takes place within condensations of mesenchymal tissue (membranes) as follows:

- In the mesenchymal membranes, ossification starts usually in the center (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.
- Several small bone masses arise in the primary ossification center, fuse to each other leaving cavities,
- The mesenchymal tissue in the cavities form capillaries, bone marrow cells, and undifferentiated cells.
- So, a sponge-like primary bone structure is formed & grows outwards.
- Finally, primary bone will be replaces by secondary bone (compact on the outer & inner surfaces & cancellous in between), forming a flat bone.



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

Clinical Notes:

The posterior fontanelles ossify within 6–8 weeks after birth. This is called intramembranous ossification. The mesenchymal connective tissue turns into bone tissue.

Anterior fontanelle is a diamond-shaped membrane-filled space located between the two frontal and two parietal bones of the developing fetal skull. It persists until approximately 18 months after birth. The fetal anterior fontanelle may be palpated until 18 months.

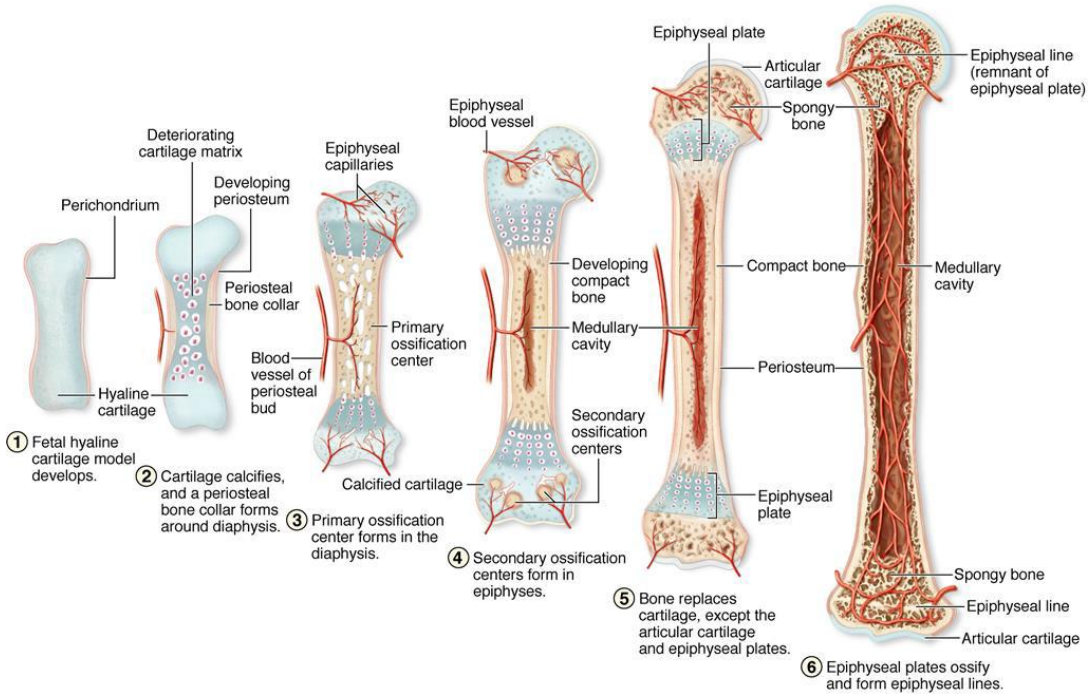
Endochondral Ossification:

Endochondral ossification takes place within a piece of hyaline cartilage whose shape resembles a small 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 cylindrical bony layer (the bone collar) surrounding the mid portion of the cartilage model. This bone collar is produced by intramembranous ossification within the local perichondrium.
- Then, the local cartilage inside the bone collar degenerates with chondrocytes apoptosis (death & enlargement) and matrix calcification, resulting in a three-dimensional structure formed by the remnants of the calcified cartilage matrix.
- Blood vessels penetrate through the bone collar 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. In this way the primary ossification center is produced.
- Then, secondary ossification centers appear at the epiphyses.
- By 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 the epiphyseal cartilage (plate) which connects the two epiphyses to the diaphysis. The epiphyseal plate is responsible for the growth in length of the bone, and it disappears (ossifies) in adults, when bone growth ceases in adulthood.

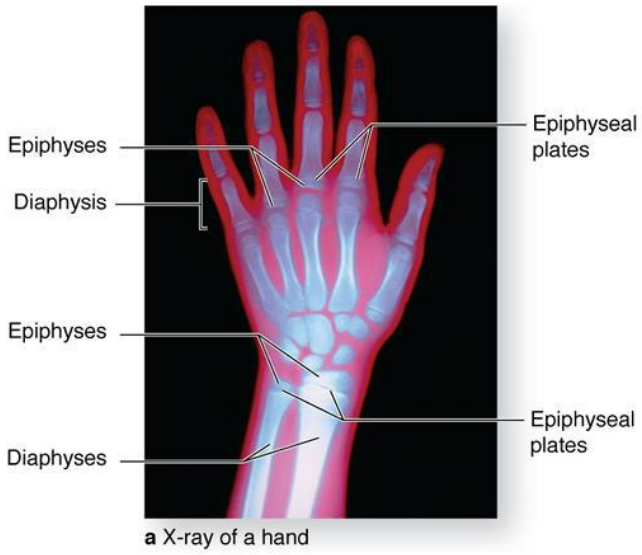


By close examination of the epiphyseal plate, it appears to be divided into 5 zones (starting from the epiphysis side):

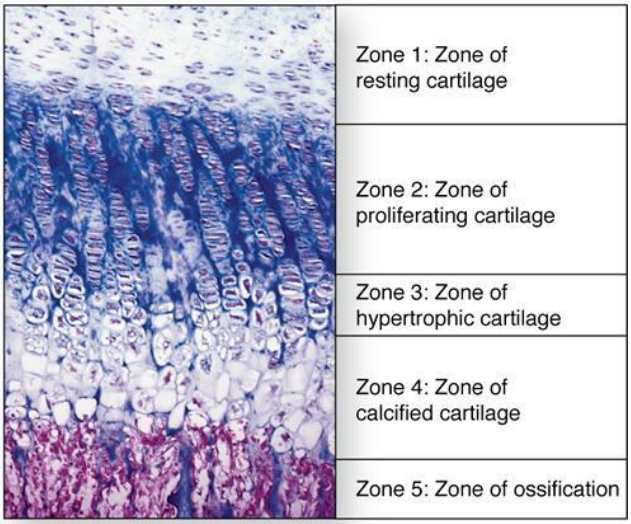
(1) The **resting zone** consists of hyaline cartilage without morphological changes in the cells.

(2) 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) The **calcified cartilage zone:** chondrocytes die, & the thin septa of cartilage matrix become calcified
(5) The **ossification zone:** endochondral bone tissue appears. Blood capillaries and osteoprogenitor cells (from the periosteum) invade the cavities left by the chondrocytes. The osteoprogenitor cells form osteoblasts, which 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, & simultaneous ossification of the plate from the diaphysis side. The rates of these two events (proliferation and destruction) are equal, so the epiphyseal plate does not change thickness. Instead, it is displaced away from the diaphysis, resulting in growth in length of the bone.

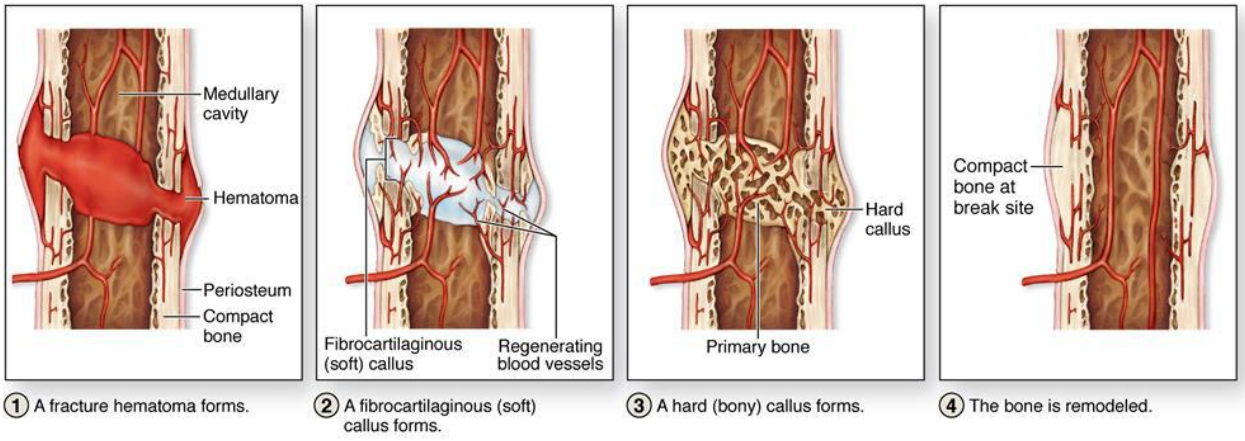


a X-ray of a hand



b Epiphyseal plate

Fracture Repair
When a bone is fractured, bone matrix is destroyed and bone cells near the fracture die. The damaged blood vessels produce a localized hemorrhage and form a blood clot.
During repair, the blood clot, cells, and damaged bone matrix are removed by macrophages. The periosteum and the endosteum around the fracture show intense proliferation producing a tissue that surrounds the fracture and fills the gap between the two bone pieces.
Primary bone is then formed by endochondral and intramembranous ossification. The irregularly formed trabeculae of primary bone temporarily unite the extremities of the fractured bone, forming a bone callus.
The primary bone tissue of the callus is gradually resorbed and replaced by secondary tissue, remodeling the bone and restoring its original structure. Unlike other connective tissues, bone tissue heals without forming a scar.



Metabolic Role of Bone Tissue

The skeleton contains 99% of the total calcium of the body and acts as a reservoir of calcium and phosphate ions. Blood calcium level is quite stable because of a continuous interchange between blood calcium and bone calcium.

Bone calcium is mobilized by two mechanisms: The first is the simple transfer of ions from bone crystals to interstitial fluid, from which calcium passes into the blood.

The second mechanism depends on hormones. Parathyroid hormone promotes osteoclastic resorption of the bone matrix with the consequent liberation of calcium. Calcitonin, from the thyroid gland, inhibits osteoclast matrix resorption, reducing calcium liberation from the bone.

Clinical notes:

Nutritional Deficiencies and Bone Remodeling

Especially during growth, bone is sensitive to nutritional factors. Calcium deficiency, which leads to incomplete calcification of the organic bone matrix, can be due either to a lack of calcium in the diet or a failure to produce the steroid prohormone vitamin D, which is important for the absorption of Ca^{+2} and PO^{-3} by the small intestine.

Calcium deficiency in children causes **rickets**, a disease in which the bone matrix does not calcify normally and the epiphyseal plate becomes distorted by the normal strains of body weight and muscular activity. Ossification processes at this level are consequently hindered, and the bones not only grow more slowly but also become deformed.

Calcium deficiency in adults gives rise to **osteomalacia** (softness), which is characterized by deficient calcification of recently formed bone and partial decalcification of already calcified matrix. Osteomalacia should not be confused with **osteoporosis**. In osteomalacia, there is a decrease in the amount of calcium per unit of bone matrix. Osteoporosis, frequently found in immobilized patients and in postmenopausal women, is an imbalance in skeletal turnover so that bone resorption exceeds bone formation.