Osteogenesis

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Osteogenesis

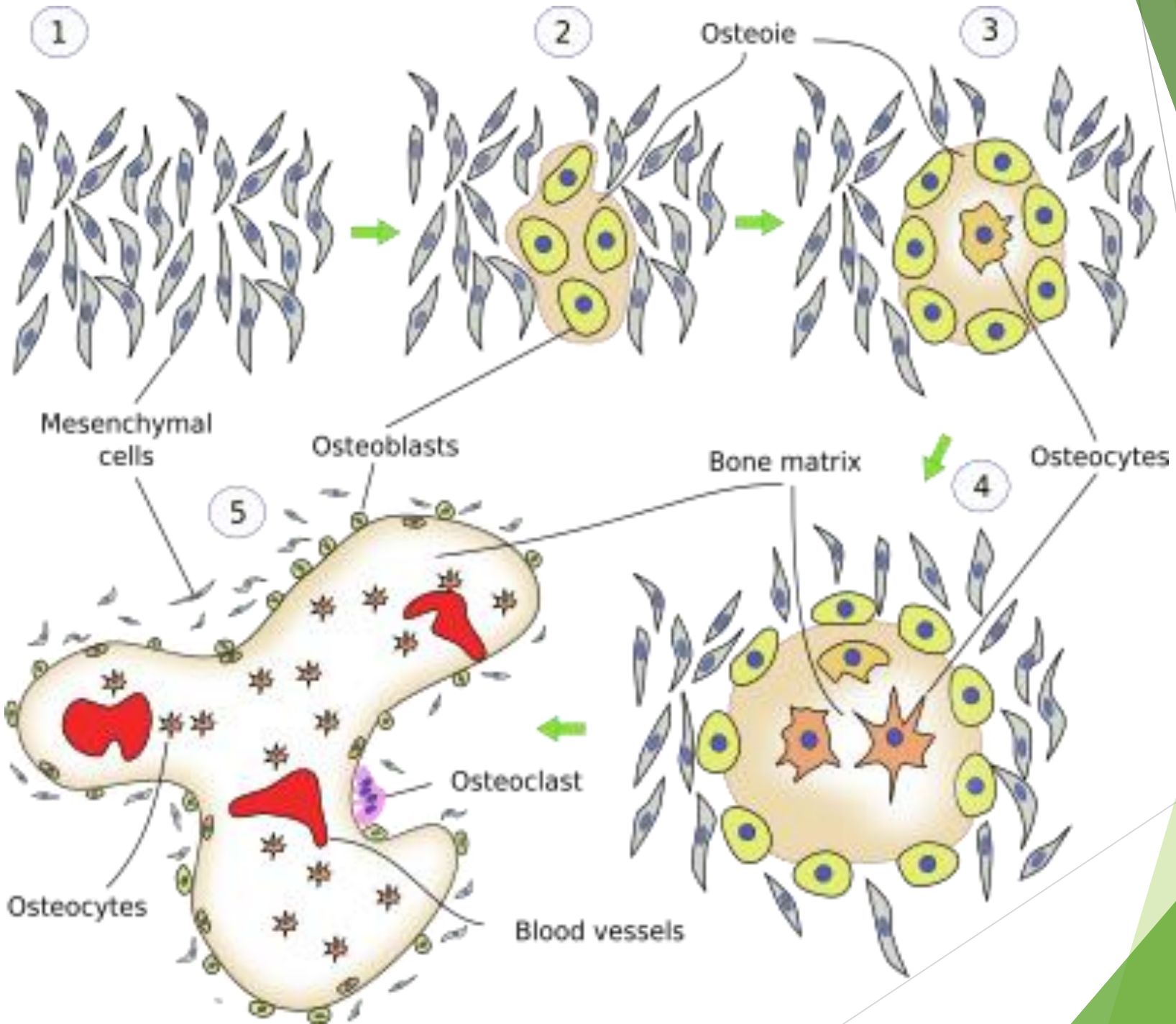
- Bone development or **osteogenesis** occurs by one of two processes:
  - **Intramembranous ossification**, in which osteoblasts differentiate directly from mesenchyme and begin secreting Osteoid
  - **Endochondral ossification**, in which a preexisting matrix of *hyaline cartilage* is eroded and invaded by osteoblasts, which then begin osteoid production.
- The names refer to the mechanisms by which the bone forms initially; in both processes woven bone is produced first and is soon replaced by stronger lamellar bone.

Intramembranous Ossification

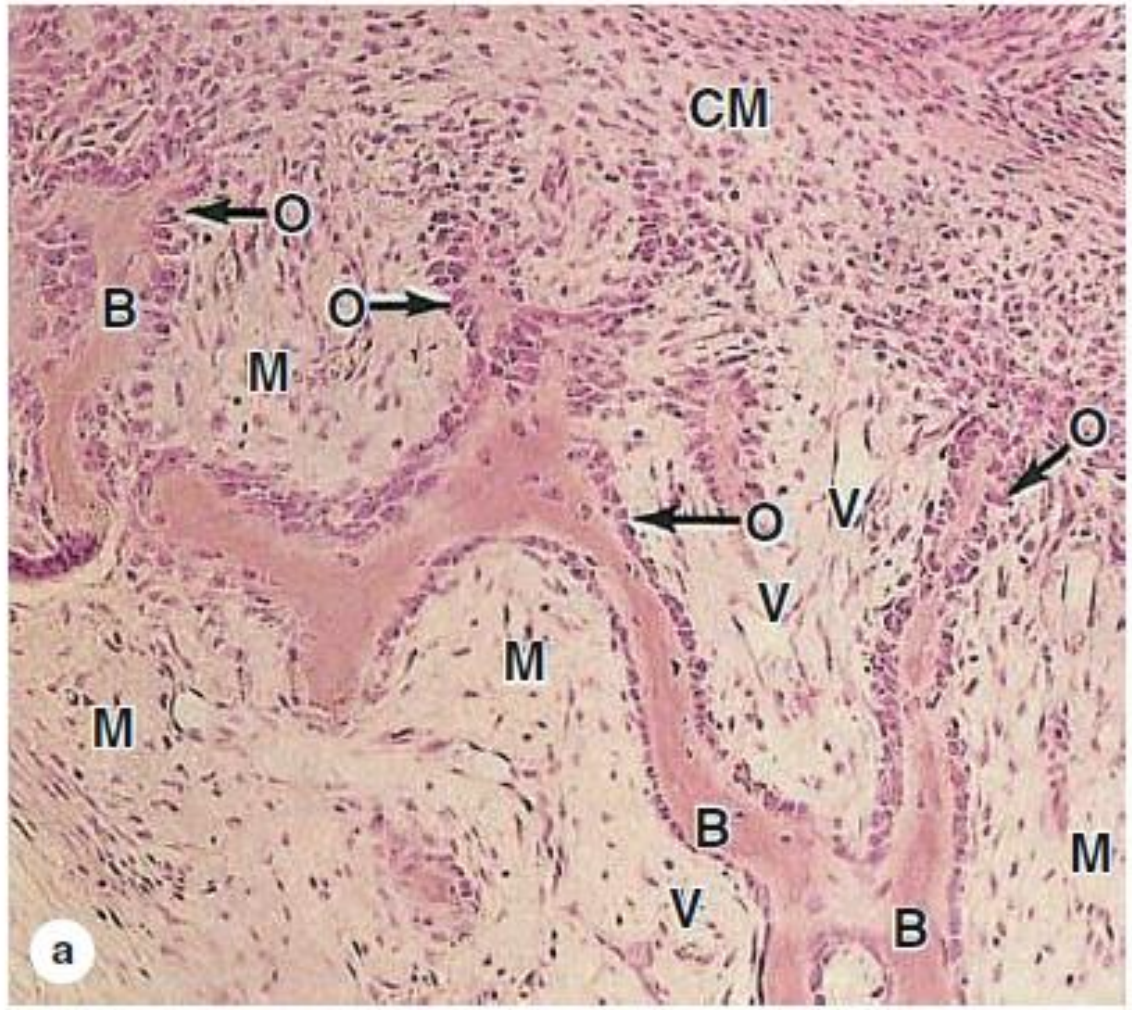
- Intramembranous ossification takes place within condensed sheets (“membranes”) of embryonic mesenchymal tissue.
- It is the process by which most flat bones begin to form
- Most bones of the skull and jaws, as well as the scapula and clavicle, are formed embryonically by intramembranous ossification.

Process of intramembranous ossification

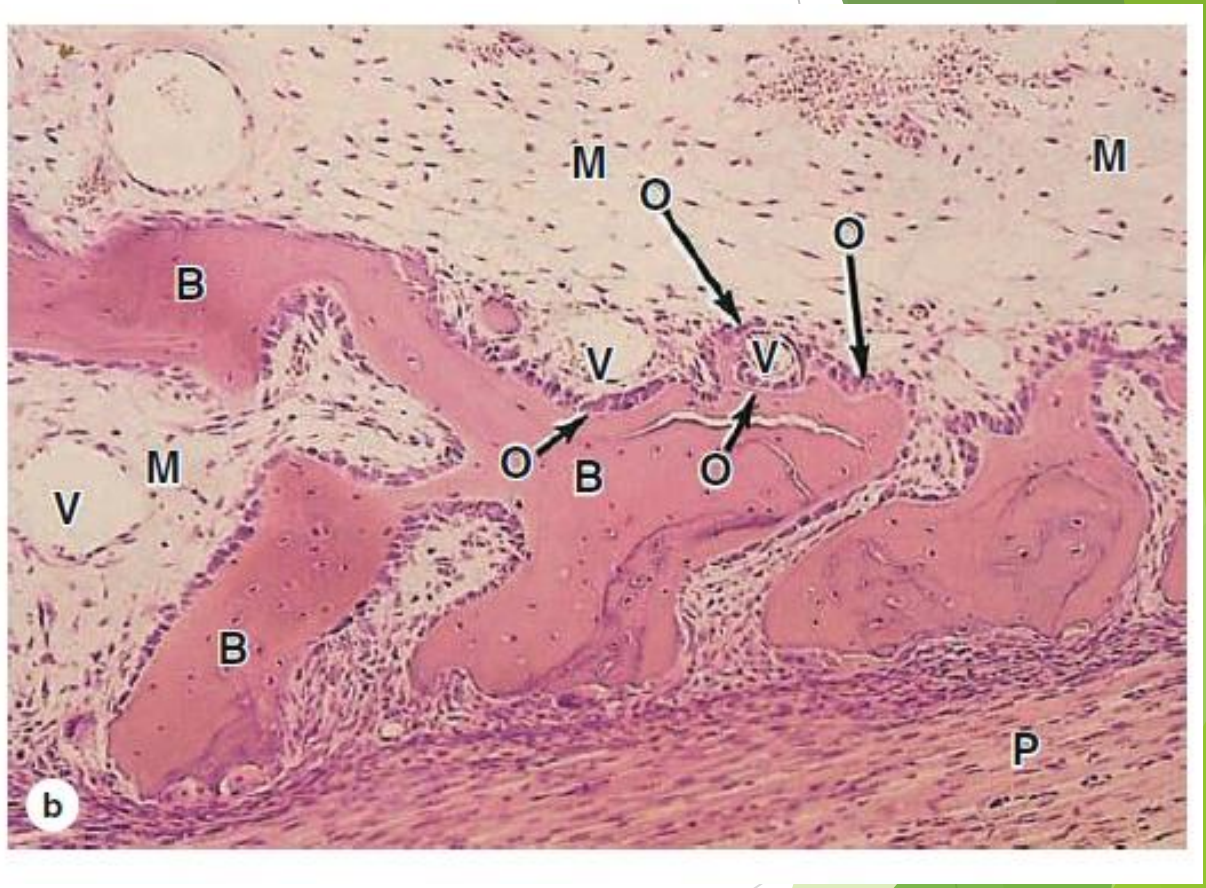
- Within the condensed mesenchyme, bone formation begins in **ossification centers**
- Ossification centers are areas in which osteoprogenitor cells arise, proliferate, and form incomplete layers of osteoblasts around a network of developing capillaries.
- Osteoid secreted by the osteoblasts calcifies, forming small irregular areas of woven bone with osteocytes in lacunae and canaliculi
- Continued matrix secretion and calcification enlarges these areas and leads to the fusion of neighboring ossification centers.
- The anatomical bone forms **gradually** as woven bone matrix is replaced by compact bone that encloses a region of cancellous bone with marrow and larger blood vessels.
- Mesenchymal regions that do not undergo ossification give rise to the endosteum and the periosteum of the new bone.


1
2
Osteoie
3
Mesenchymal cells
Osteoblasts
Bone matrix
Osteocytes
4
5
Osteoclast
Osteocytes
Blood vessels

- A section of fetal mandible developing by intramembranous ossification. **(a)** Areas of typical mesenchyme (**M**) and condensed mesenchyme (**CM**) are adjacent to layers of new osteoblasts (**O**). Some osteoblasts have secreted matrices of bone (**B**), the surfaces of which remain covered by osteoblasts. Between these thin regions of new woven bone are areas with small blood vessels (**V**).

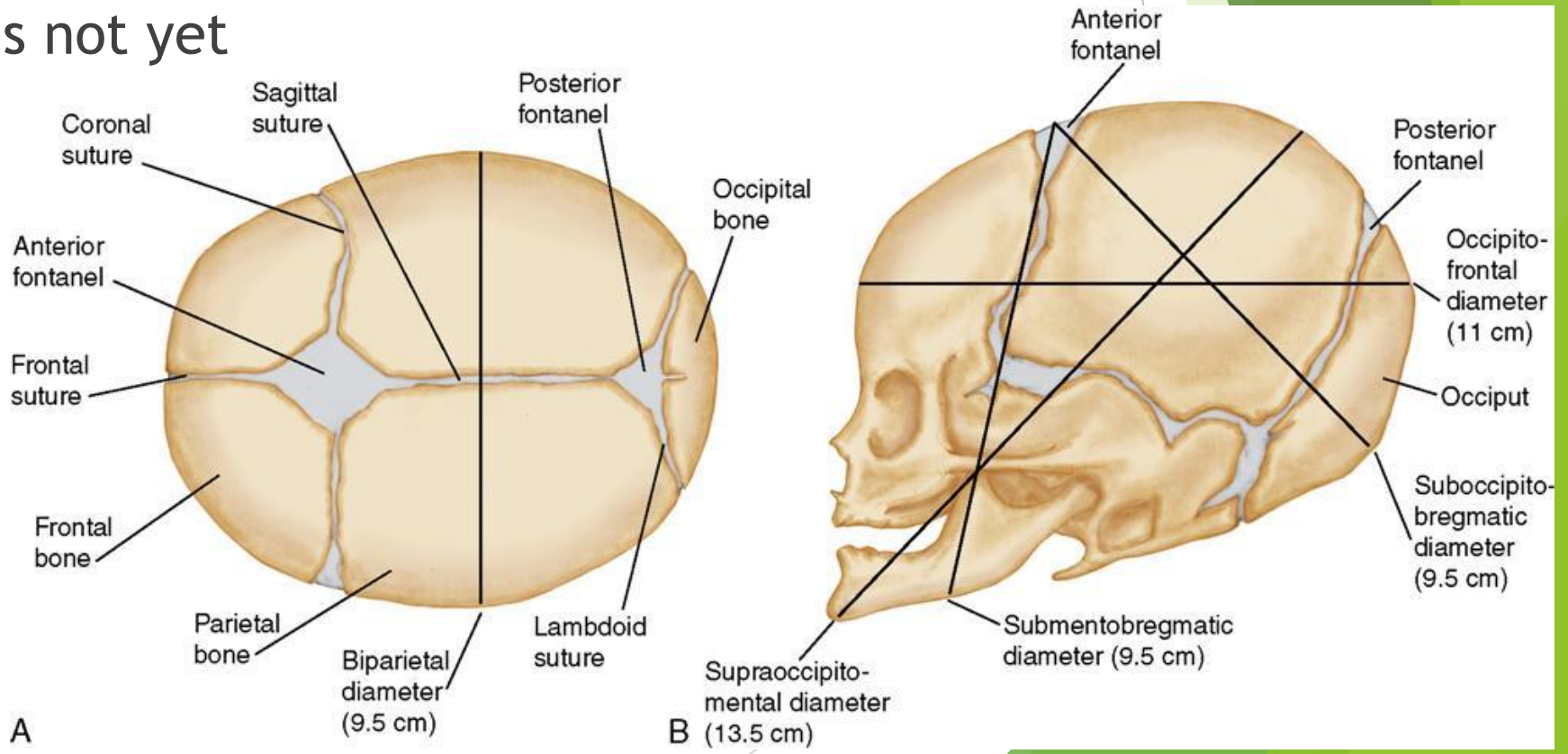


- **(b)** At higher magnification another section shows these same structures, but also includes the developing periosteum (**P**) adjacent to the masses of woven bone that will soon merge to form a continuous plate of bone. The larger mesenchyme-filled region at the top is part of the developing marrow cavity. Osteocytes in lacunae can be seen within the bony matrix.



Fontanelles

- The fontanelles or “soft spots” on the heads of newborn infants are areas of the skull in which the membranous tissue is not yet ossified.

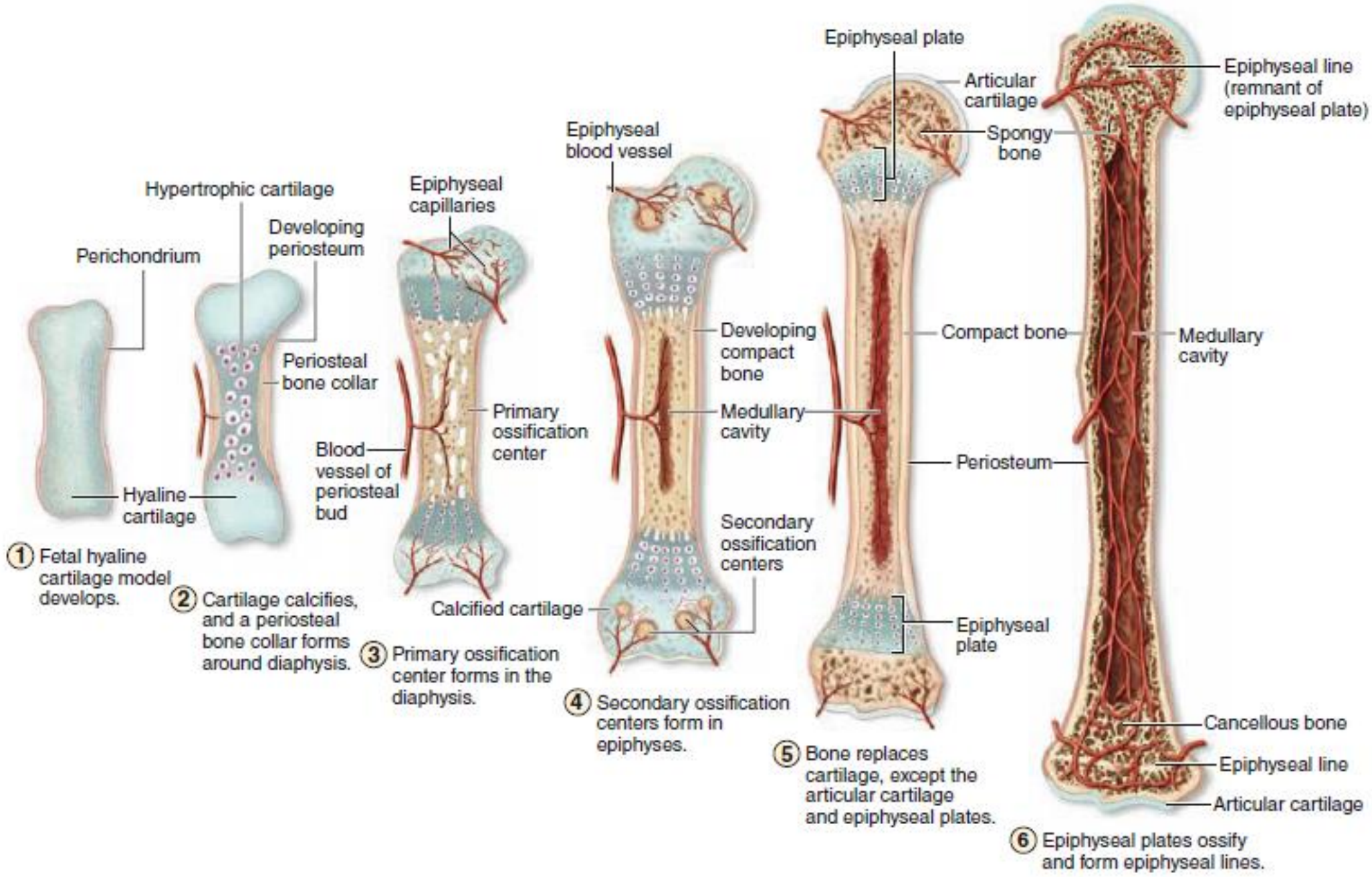


Endochondral Ossification

- Endochondral ossification takes place within hyaline cartilage shaped as a small version, or model, of the bone to be formed.
- This type of ossification forms most bones of the body and is especially well studied in developing long bones, where it consists of a sequence of events

Process of endochondral ossification

- Ossification first occurs within a **bone collar** produced by osteoblasts that differentiate within the perichondrium (transitioning to periosteum) around the cartilage model diaphysis.
- The collar impedes diffusion of oxygen and nutrients into the underlying cartilage, causing local chondrocytes to swell up (hypertrophy), compress the surrounding matrix, and initiate its calcification by releasing osteocalcin and alkaline phosphatase.
- The hypertrophic chondrocytes eventually die, creating empty spaces within the calcified matrix.
- One or more blood vessels from the perichondrium (now the periosteum) penetrate the bone collar, bringing osteoprogenitor cells to the porous central region.
- Along with the vasculature newly formed osteoblasts move into all available spaces and produce woven bone.
- The remnants of calcified cartilage at this stage are basophilic and the new bone is more acidophilic


Perichondrium
Hyaline cartilage
Hypertrophic cartilage
Developing periosteum
Periosteal bone collar
Blood vessel of periosteal bud
Epiphyseal capillaries
Primary ossification center
Calcified cartilage
Epiphyseal blood vessel
Developing compact bone
Medullary cavity
Secondary ossification centers
Epiphyseal plate
Articular cartilage
Spongy bone
Compact bone
Periosteum
Epiphyseal plate
Epiphyseal line (remnant of epiphyseal plate)
Medullary cavity
Cancellous bone
Epiphyseal line
Articular cartilage
1 Fetal hyaline cartilage model develops.
2 Cartilage calcifies, and a periosteal bone collar forms around diaphysis.
3 Primary ossification center forms in the diaphysis.
4 Secondary ossification centers form in epiphyses.
5 Bone replaces cartilage, except the articular cartilage and epiphyseal plates.
6 Epiphyseal plates ossify and form epiphyseal lines.

Primary and secondary ossification centers

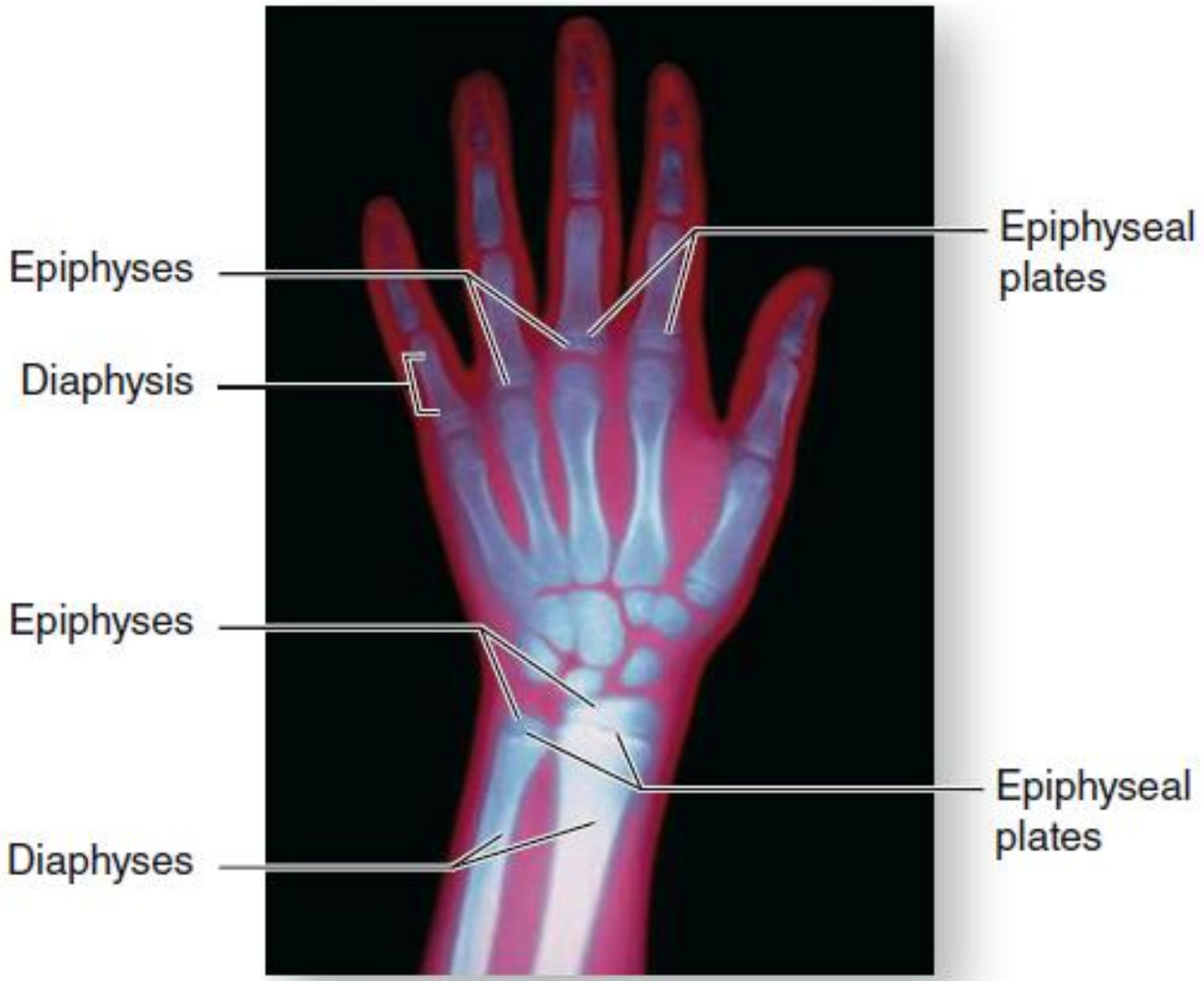
- This process in the diaphysis forms the **primary ossification center,** beginning in many embryonic bones as early as the first trimester.
- **Secondary ossification centers** appear later at the epiphyses of the cartilage model and develop in a similar manner.
- During their expansion and remodeling both the primary and secondary ossification centers produce cavities that are gradually filled with bone marrow and trabeculae of cancellous bone

Cartilage associated with bone

- With the primary and secondary ossification centers, two regions of cartilage remain:
  - **Articular cartilage** within the joints between long bones, which normally persists through adult life
  - The specially organized **epiphyseal cartilage** (also called the **epiphyseal plate** or growth plate), which connects each epiphysis to the diaphysis and allows longitudinal bone growth

Epiphyseal cartilage

- The epiphyseal cartilage is responsible for the growth in length of the bone and disappears upon completion of bone development at adulthood.
- Elimination of these epiphyseal plates ("epiphyseal closure") occurs at various times with different bones and by about age 20 is complete in all bones, making further growth in bone length no longer possible.
- In forensics or through x-ray examination of the growing skeleton, it is possible to determine the "bone age" of a young person, by noting which epiphyses have completed closure.

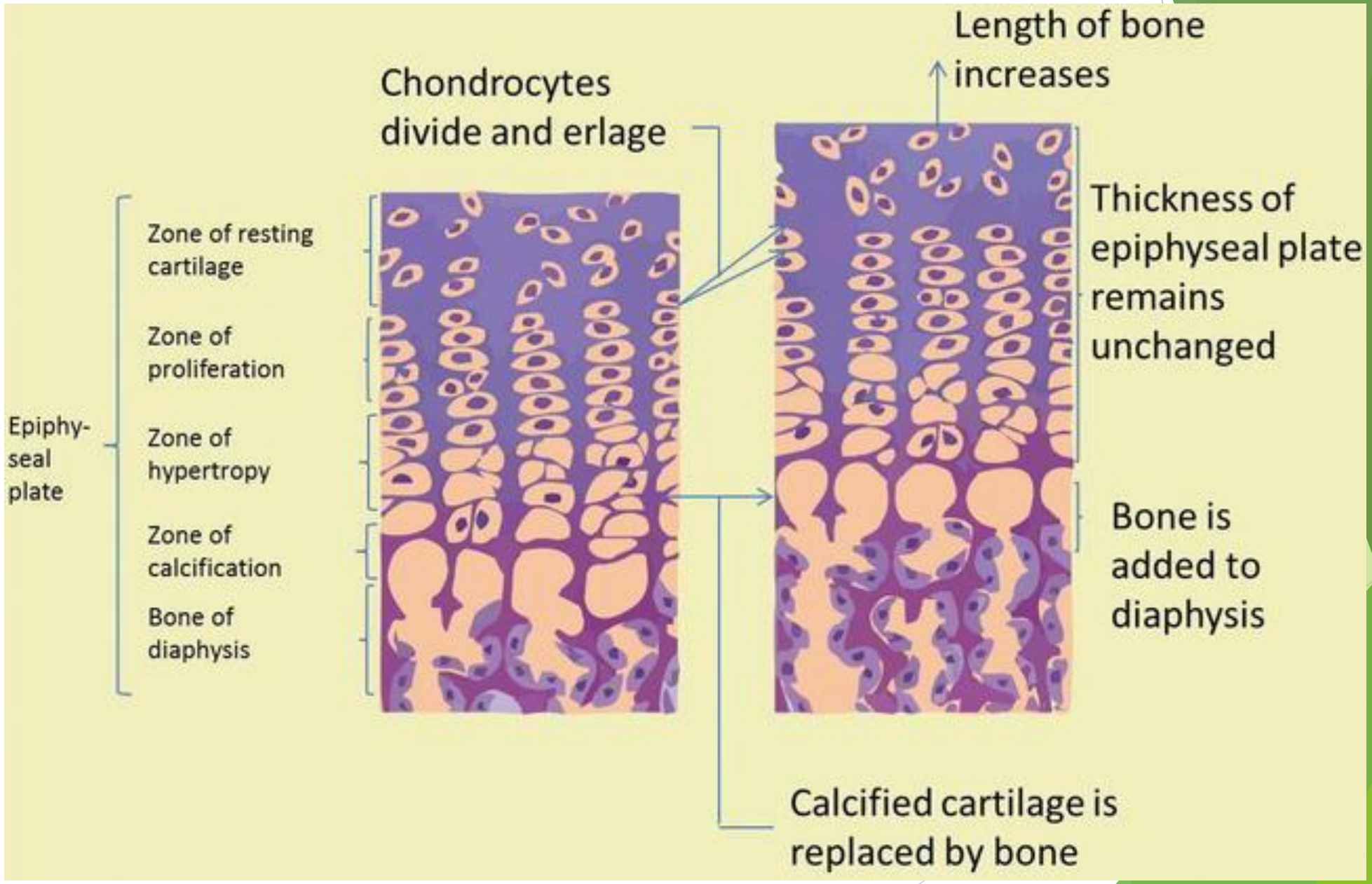


a X-ray of a hand

Epiphyseal growth plate zones

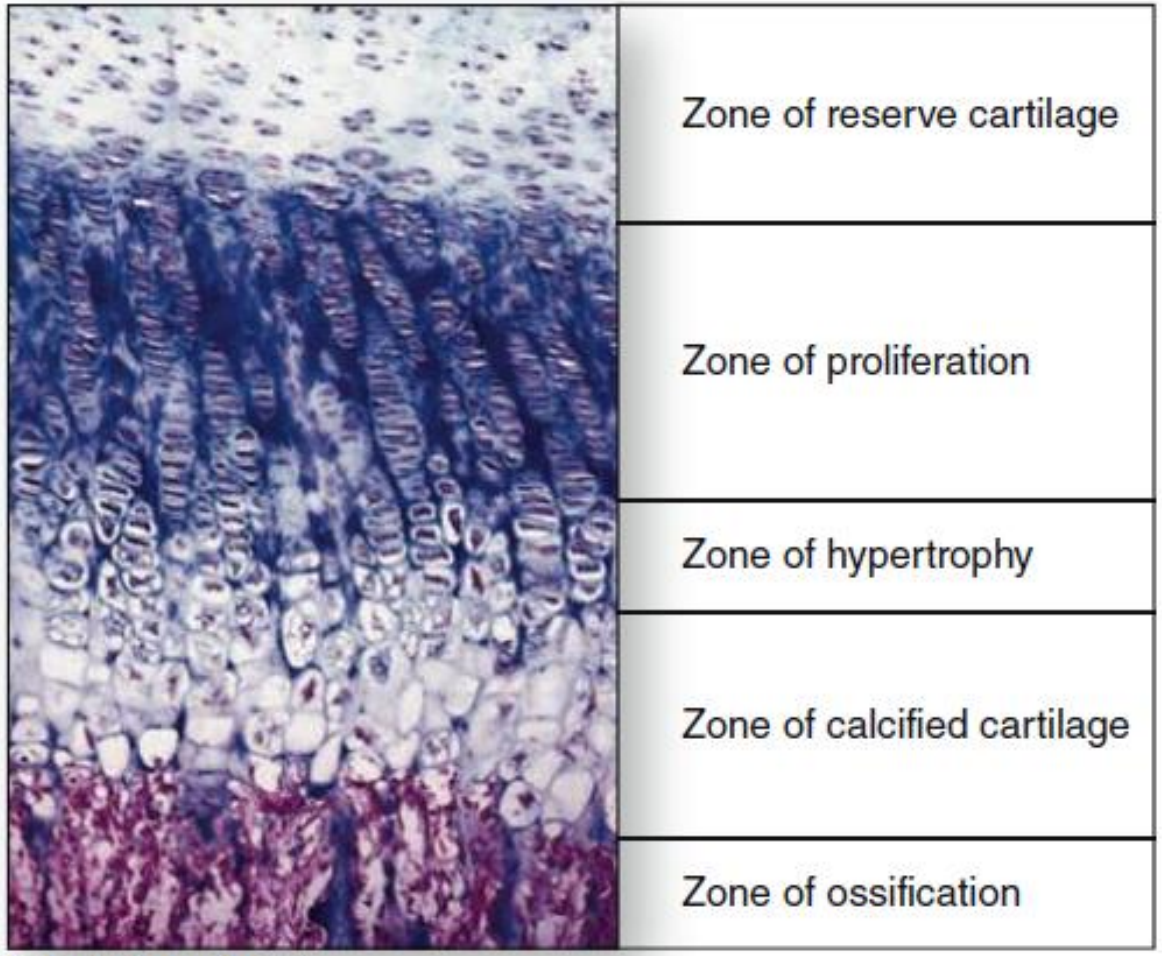
- An epiphyseal growth plate shows distinct regions of cellular activity and is often discussed in terms of overlapping but histologically distinct zones starting with the cartilage farthest from the ossification center in the diaphysis:

1. The **zone of reserve** (or **resting**) **cartilage**
2. The **proliferative zone**
3. The **zone of hypertrophy**
4. The **zone of calcified cartilage**
5. The **zone of ossification**


Length of bone increases
Chondrocytes divide and erlage
Epiphy-seal plate
Zone of resting cartilage
Zone of proliferation
Zone of hypertropy
Zone of calcification
Bone of diaphysis
Thickness of epiphyseal plate remains unchanged
Bone is added to diaphysis
Calcified cartilage is replaced by bone

Zone of resting cartilage

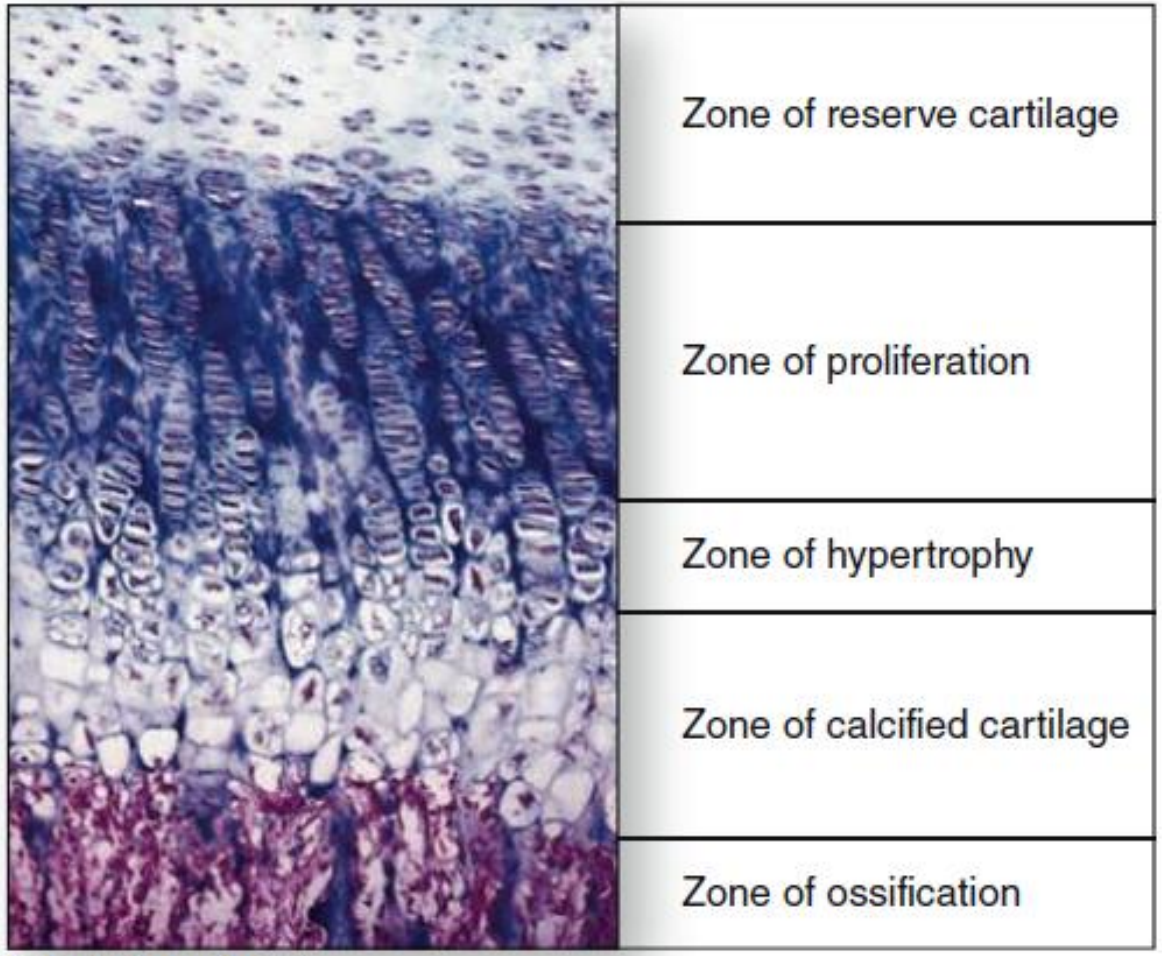
- The **zone of reserve** (or **resting**) **cartilage** is composed of typical hyaline cartilage.
- It is the farthest zone from the diaphysis ossification center



b Epiphyseal plate

Proliferative zone

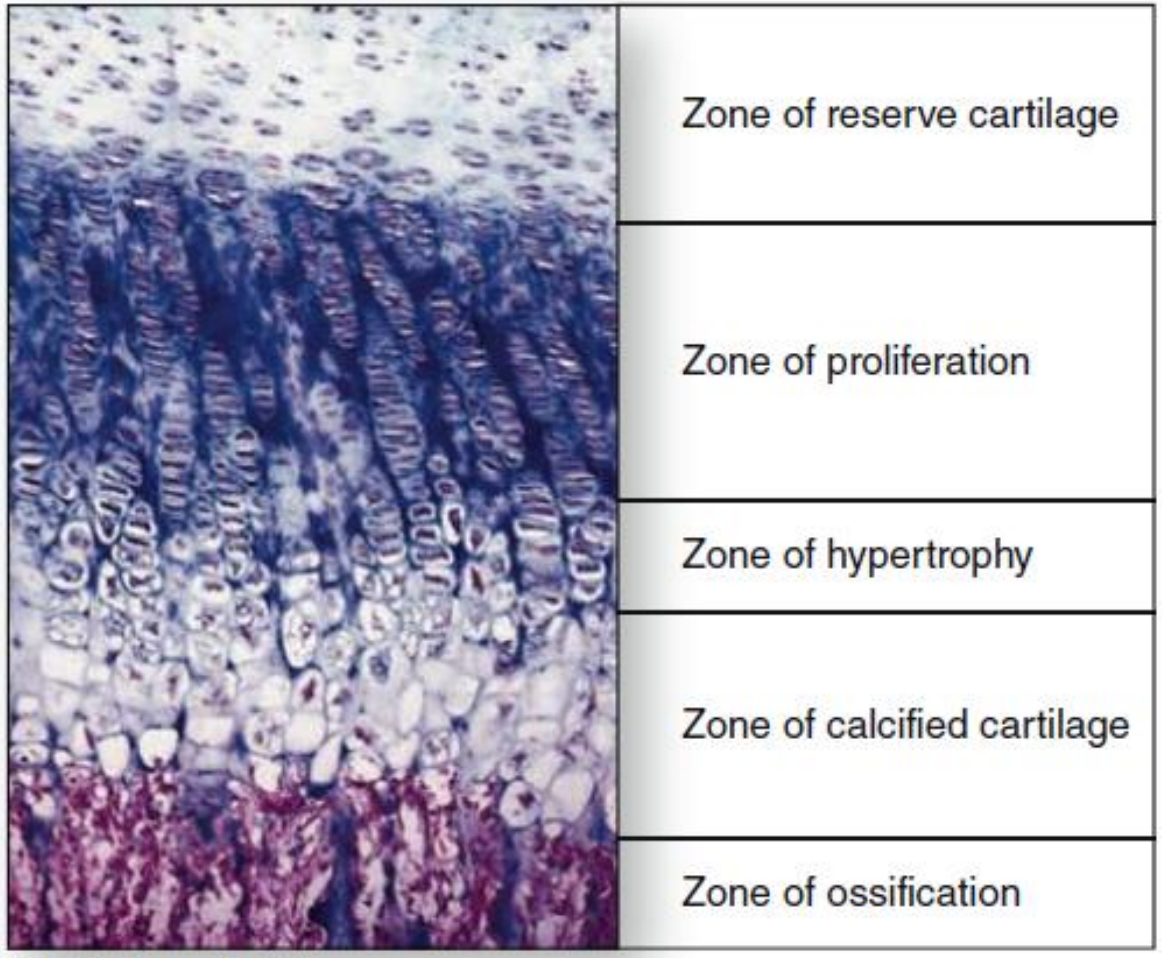
- In the **proliferative zone**, the cartilage cells divide repeatedly, enlarge and secrete more type II collagen and proteoglycans, and become organized into columns parallel to the long axis of the bone.



b Epiphyseal plate

Zone of hypertrophy

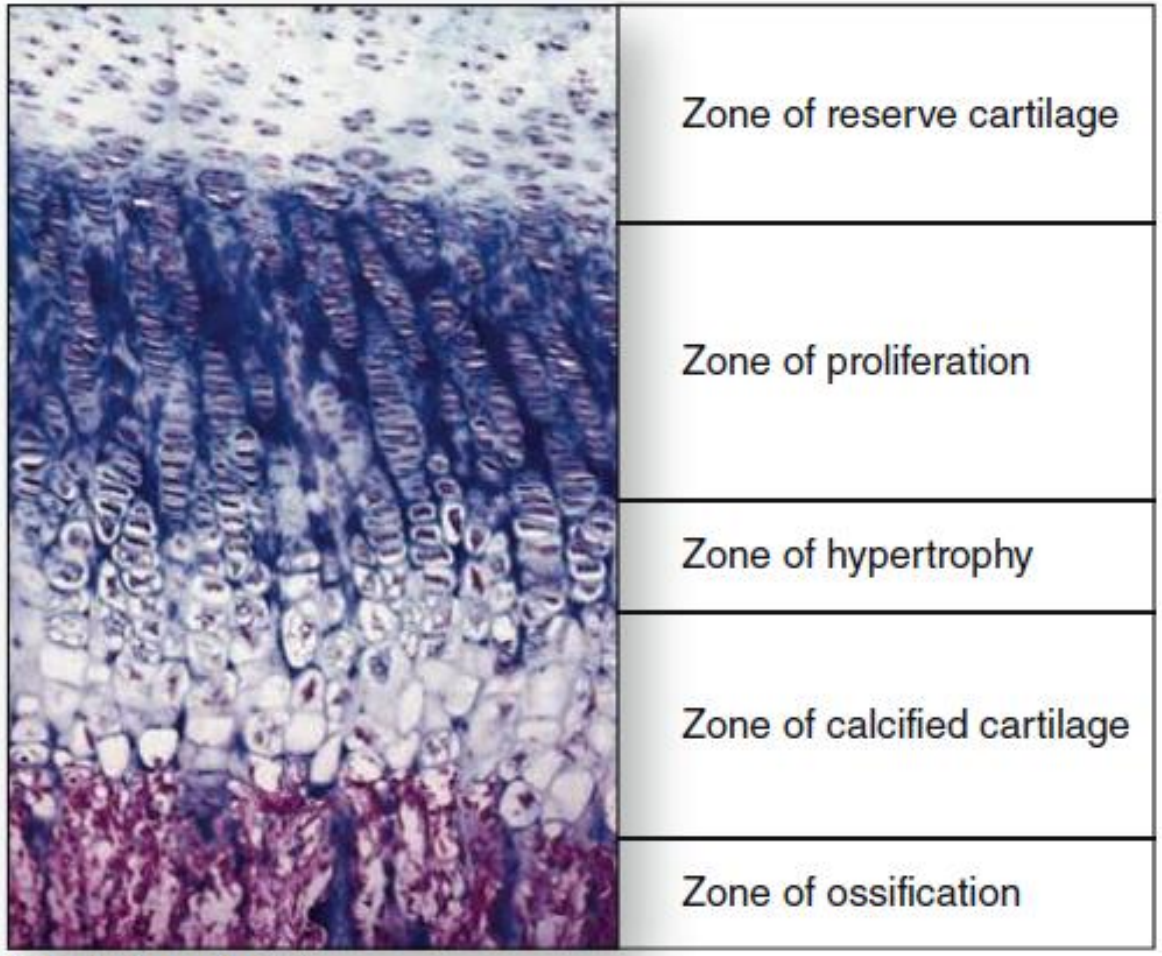
- The **zone of hypertrophy** contains swollen, terminally differentiated chondrocytes which compress the matrix into aligned spicules and stiffen it by secretion of type X collagen.
- Unique to the hypertrophic chondrocytes in developing (or fractured) bone, type X collagen limits diffusion in the matrix and with growth factors promotes vascularization from the adjacent primary ossification center



b Epiphyseal plate

The zone of calcified cartilage

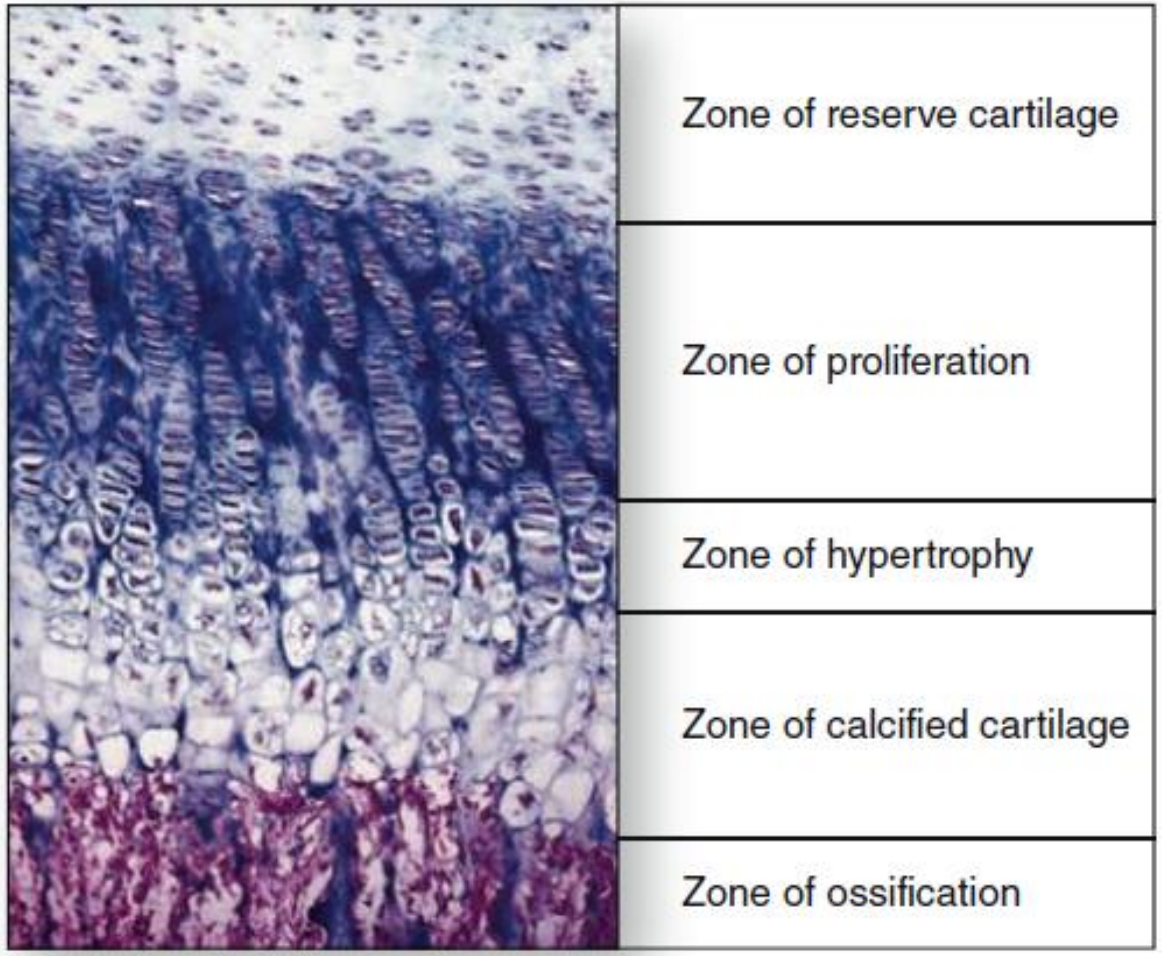
- In the **zone of calcified cartilage** chondrocytes about to undergo apoptosis release matrix vesicles and osteocalcin to begin matrix calcification by the formation of hydroxyapatite crystals.



b Epiphyseal plate

Zone of ossification

- In the **zone of ossification** bone tissue first appears.
- Capillaries and osteoprogenitor cells invade the now vacant chondrocytic lacunae, many of which merge to form the initial marrow cavity.
- Osteoblasts settle in a layer over the calcified cartilage matrix and secrete osteoid which becomes woven bone
- This woven bone is then remodeled as lamellar bone.

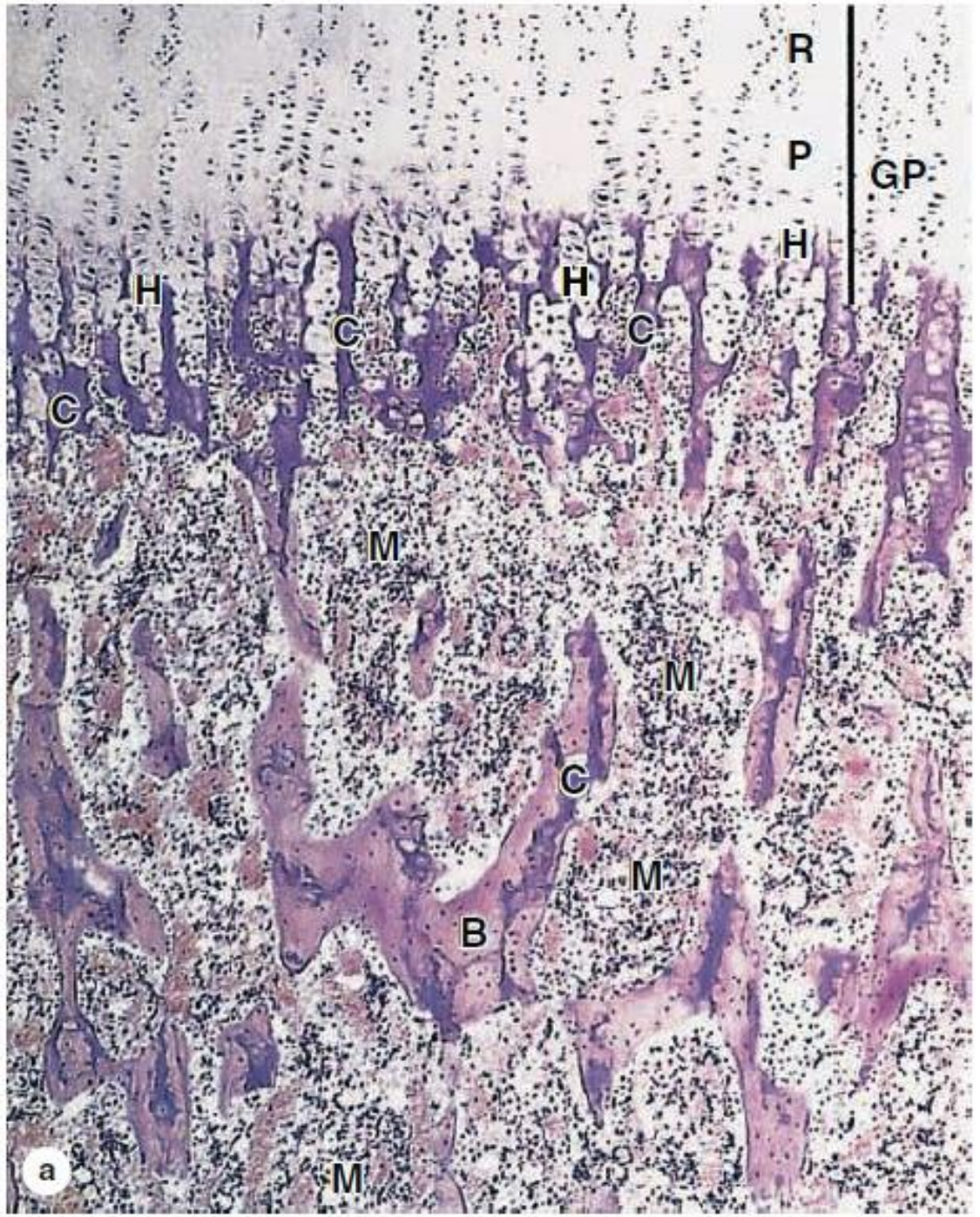


b Epiphyseal plate

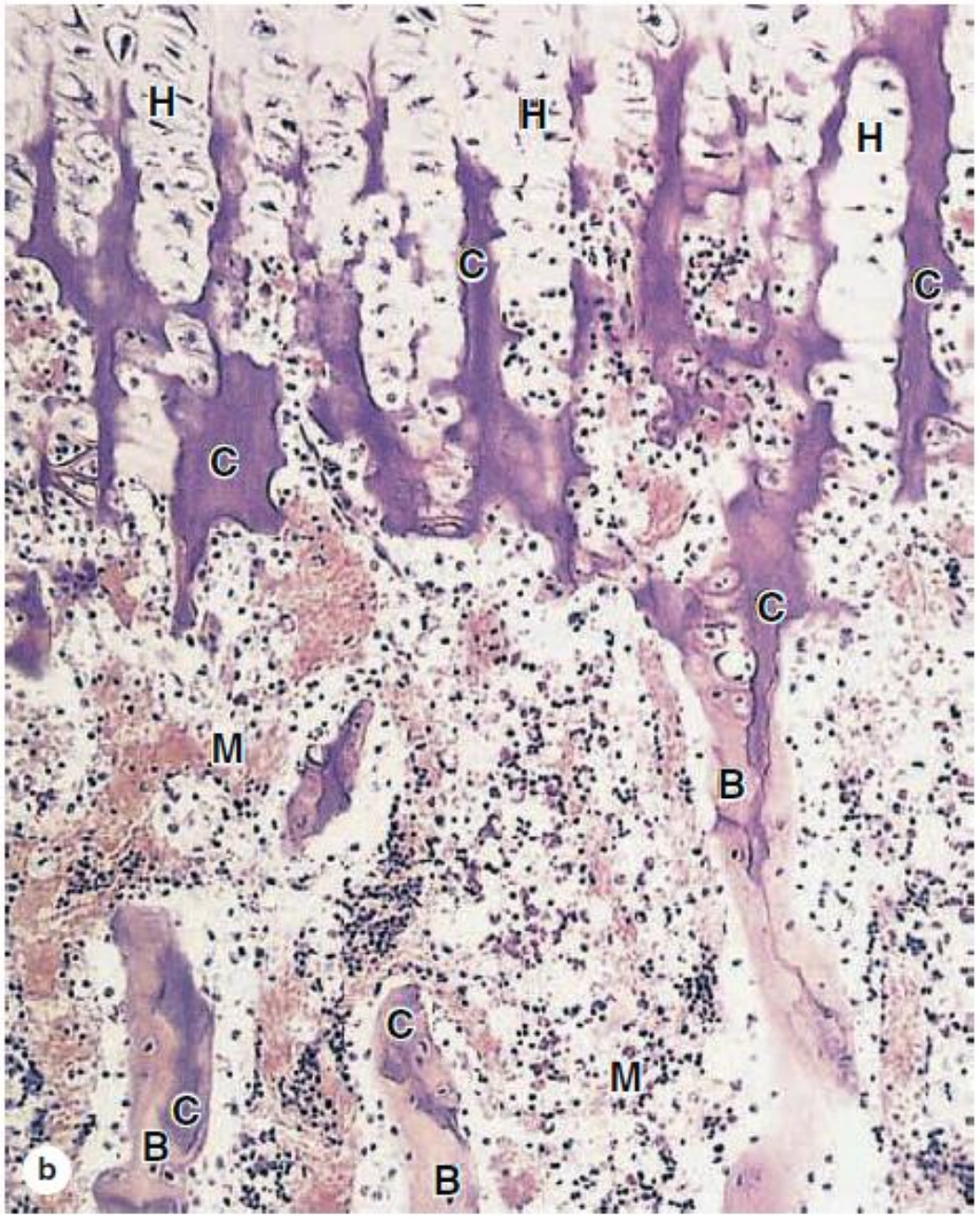
Longitudinal bone growth

- In summary, longitudinal growth of a bone occurs by cell proliferation in the epiphyseal plate cartilage.
- At the same time, chondrocytes in the diaphysis side of the plate undergo hypertrophy, their matrix becomes calcified, and the cells die.
- Osteoblasts lay down a layer of new 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, but is instead displaced away from the center of the diaphysis as the length of the bone increases.

- **(a)** At the top of the micrograph the growth plate (**GP**) shows its zones of hyaline cartilage with chondrocytes at rest (**R**), proliferating (**P**), and hypertrophying (**H**).
- As the chondrocytes swell they release type X collagen, which initiates hydroxyapatite formation and strengthens the adjacent calcifying spicules (**C**) of old cartilage matrix.
- The tunnel-like lacunae in which the chondrocytes have undergone apoptosis are invaded from the diaphysis by capillaries that begin to convert these spaces into marrow (**M**) cavities.
- Endosteum with osteoblasts also moves in from the diaphyseal primary ossification center, covering the spicules of calcified cartilage and laying down layers of osteoid to form a matrix of woven bone (**B**).

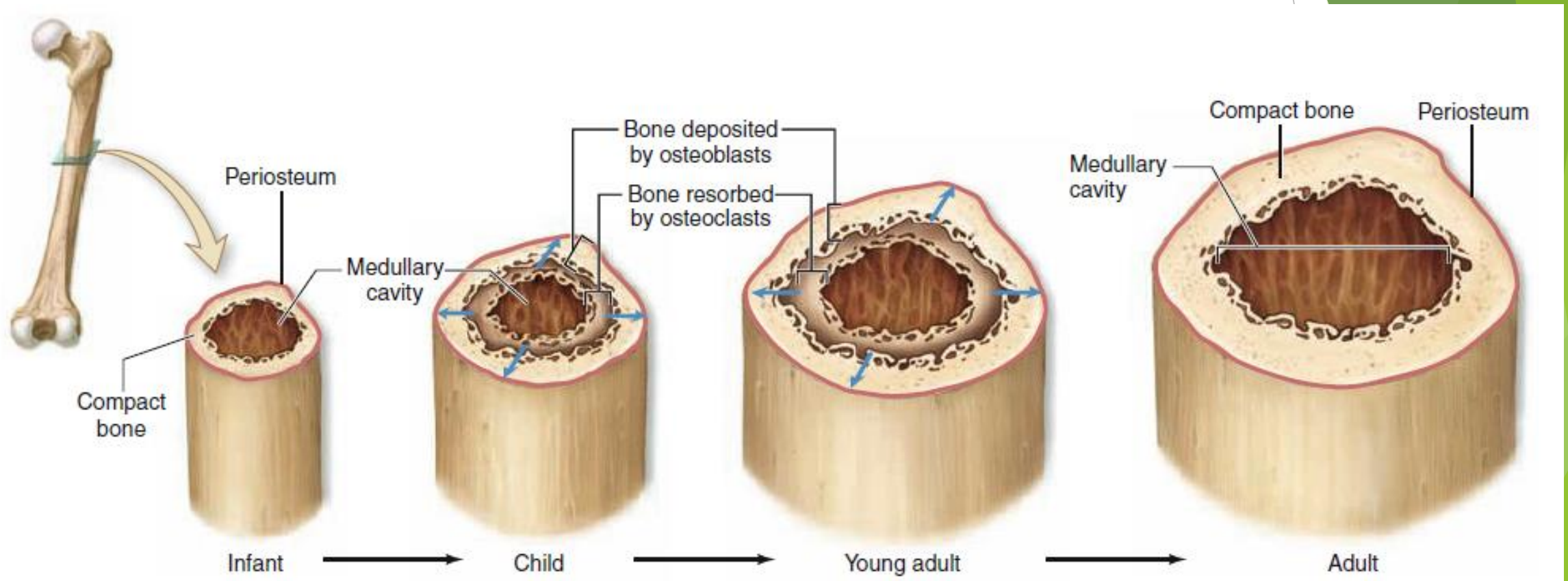


- **(b)** Higher magnification shows more detail of the cells and matrix spicules in the zones undergoing hypertrophy (**H**) and ossification.
- Staining properties of the matrix clearly change as it is compressed and begins to calcify (**C**), and when osteoid and bone (**B**) are laid down.
- The large spaces between the ossifying matrix spicules become the marrow cavity (**M**), in which pooled masses of eosinophilic red blood cells and aggregates of basophilic white blood cell precursors can be distinguished.



Thickening of bones

- Growth in the circumference of long bones does not involve endochondral ossification but occurs through the activity of osteoblasts developing from osteoprogenitor cells in the periosteum by a process of **appositional growth**
- Increasing bone circumference is accompanied by enlargement of the central marrow cavity by the activity of osteoclasts in the endosteum


Periosteum
Medullary cavity
Compact bone
Bone deposited by osteoblasts
Bone resorbed by osteoclasts
Compact bone
Periosteum
Medullary cavity
Infant
Child
Young adult
Adult