# DEVELOPMENT OF AXIAL SKELETON

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# OBJECTIVES

- Understand the components of axil skeleton
- Understand the development of various components of axial skeleton
- Understand congenital malformations associated with axial skeleton development

# The Skeleton

- Consists of
  - Bones, cartilage, joints, and ligaments
- Composed of 206 named bones: two divisions
  - Axial skeleton (80 bones)
  - Appendicular skeleton (126 bones)

# The Axial Skeleton

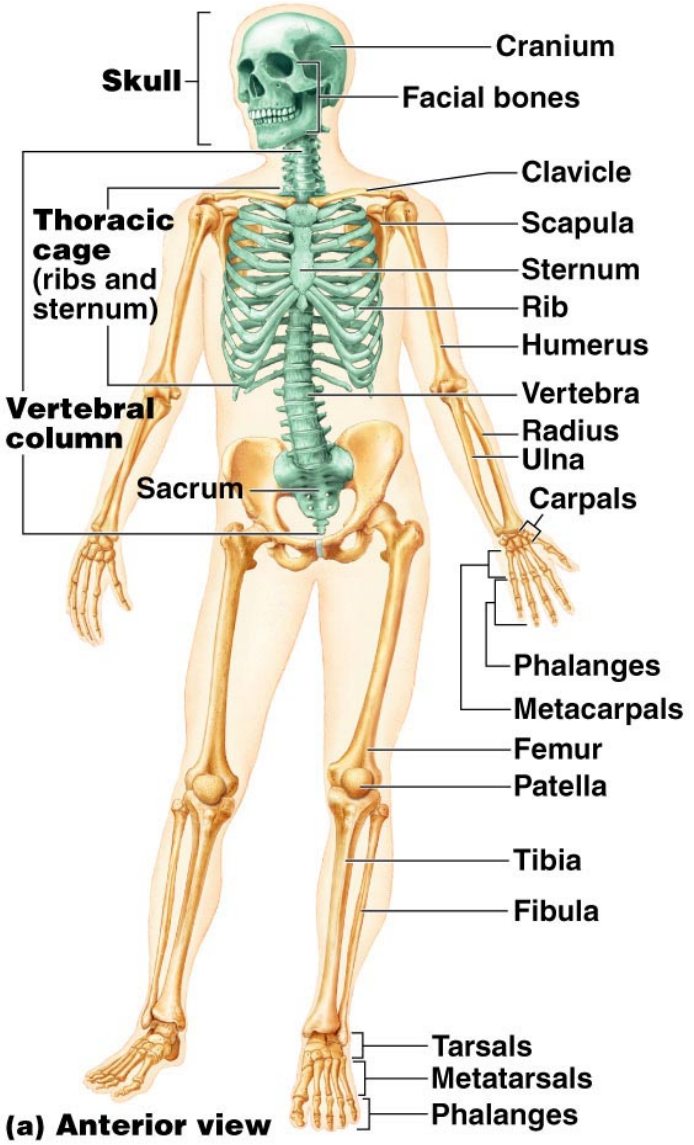
- The axial skeleton
  - **The vertebral column**
    - 24 vertebrae (singular = vertebra)
    - The sacrum
    - The coccyx
  - **The thoracic cage**
    - 24 ribs
    - The sternum

# The Axial Skeleton

- The **axial skeleton**
  - Forms the longitudinal axis of the body
  - Has 80 bones
    - **The skull**:
      - 8 **cranial bones**
      - 14 **facial bones**
    - **Bones associated with the skull:**
      - 6 **auditory ossicles**
      - the **hyoid bone**

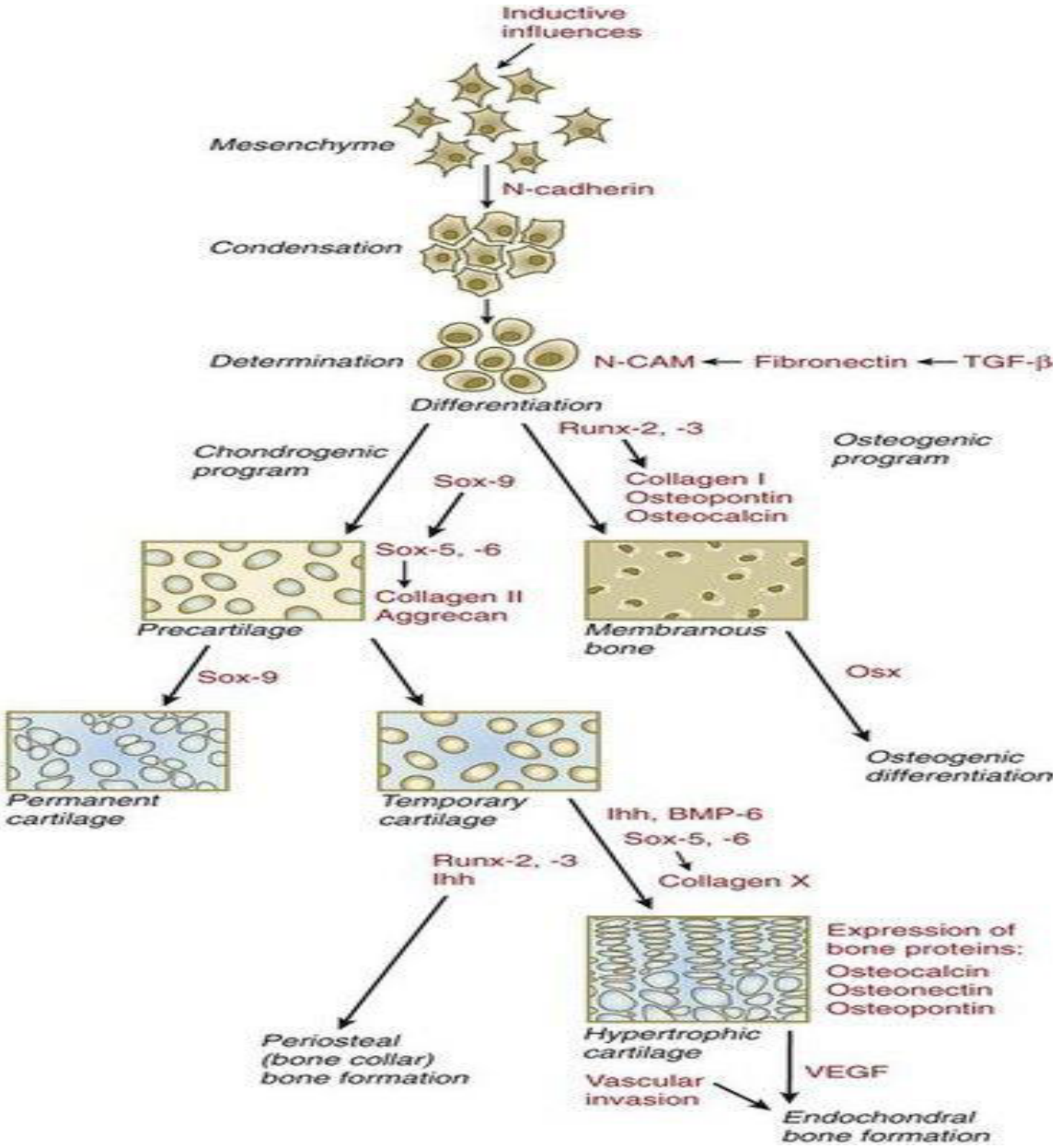
# The Axial Skeleton

- Formed from 80 named bones
- Consists of skull, vertebral column, and bony thorax



# INTRODUCTION

- The axial skeleton is composed of the:
  - cranium (skull),
  - vertebral column,
  - ribs,
  - sternum
- A**xial skeleton** originates from:
  - the sclerotomal portion of the mesodermal somites
  - Neural crest cells
- The appendicular skeleton (the bones of the limbs and their respective girdles) is derived from the mesenchyme of the lateral plate mesoderm.
- There is positional change of the sclerotomal cells effected by differential growth of the surrounding structures.
- The Hox and Pax genes regulate the patterning and regional development of the vertebrae along the anterior-posterior axis.

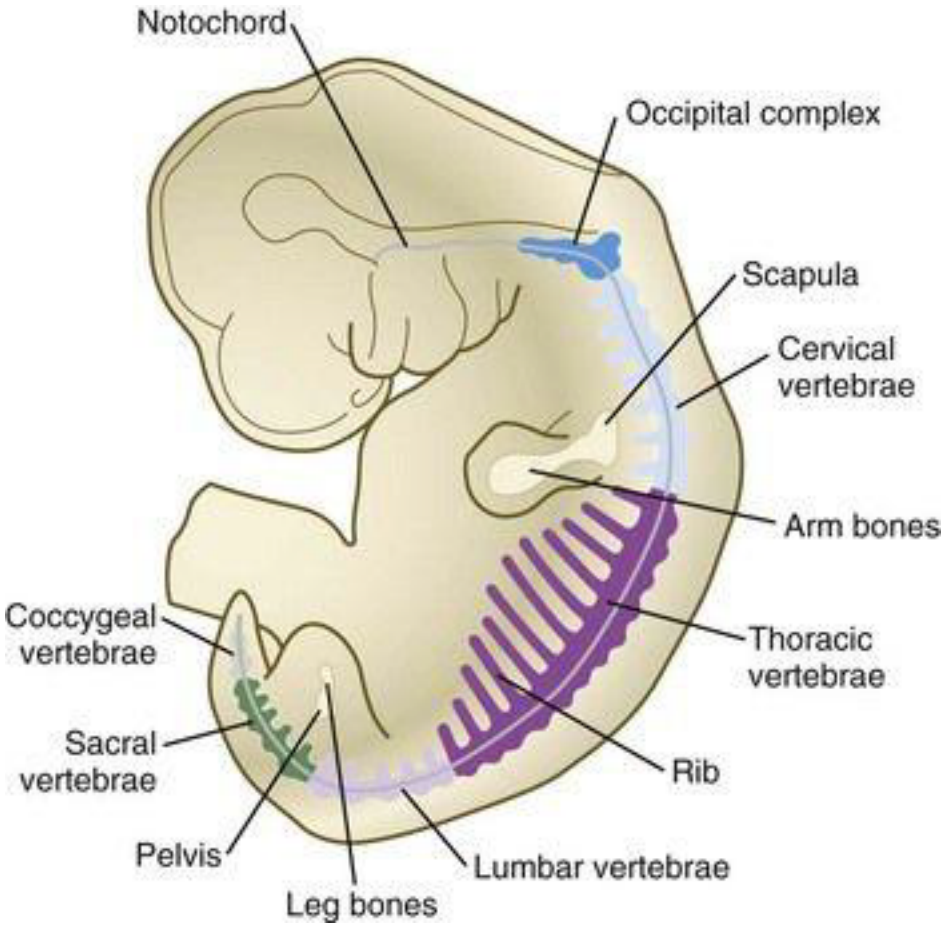



Major steps in the differentiation of bone and cartilage

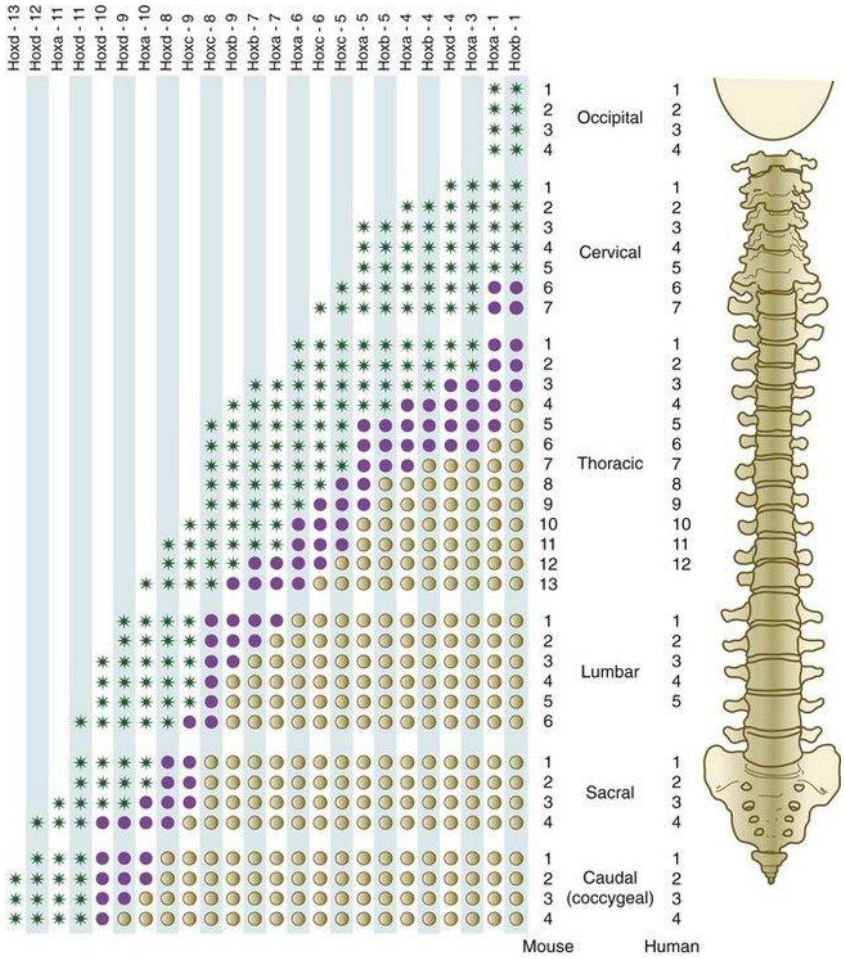
# SKELETOGENESIS

- An inductive interaction between the sclerotome and notochord or neural tube initiates **skeletogenesis** of the vertebral column.
- In the head, preskeletal cells of the neural crest may receive information at levels ranging from:
  - the neural tube itself
  - to sites along their path of migration
  - to the region of their final destination
- Inductive interactions between regions of the brain and the overlying mesenchyme stimulate formation of the membrane bones of the cranial vault.

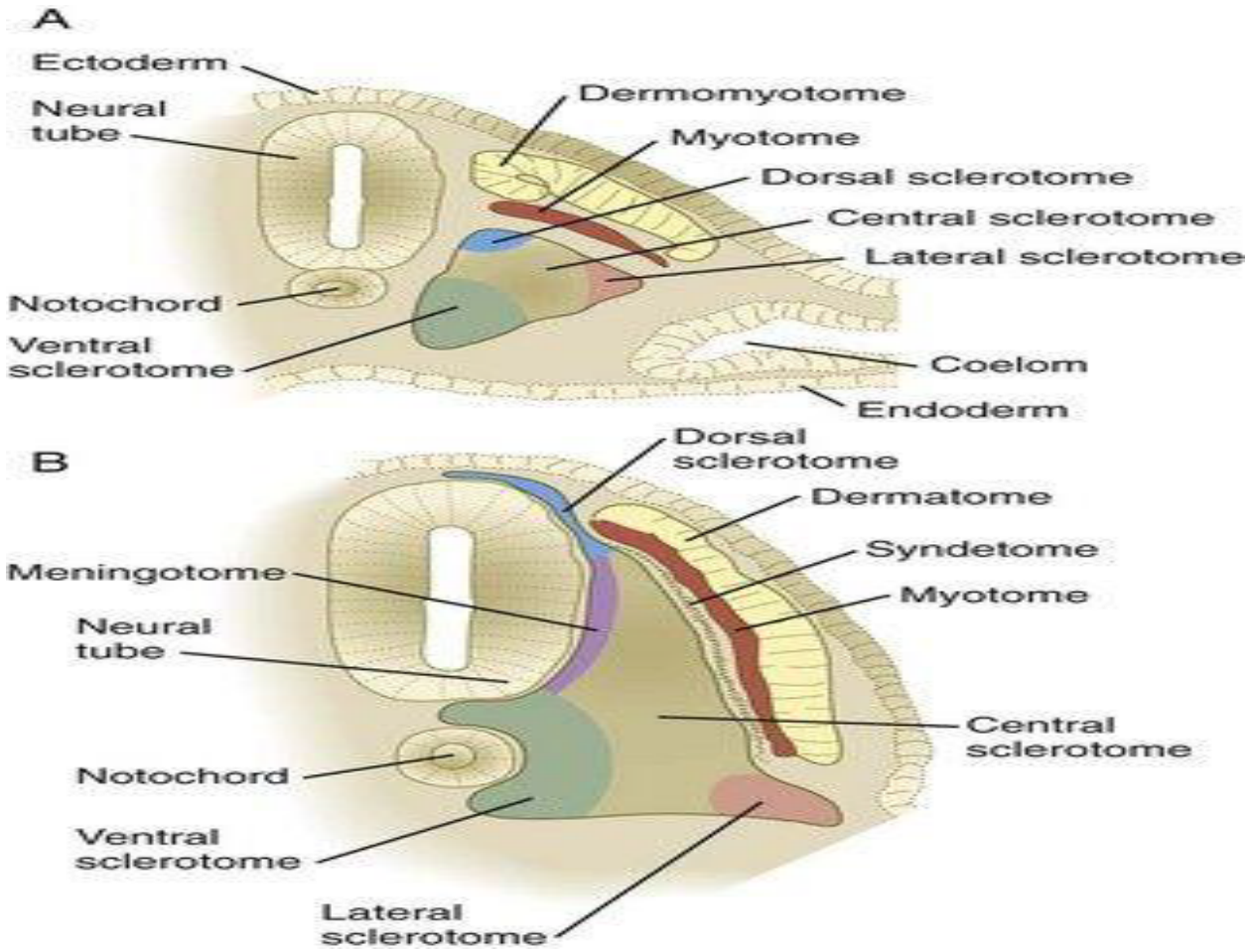
# Precartilaginous primordia in the 9-mm long human embryo

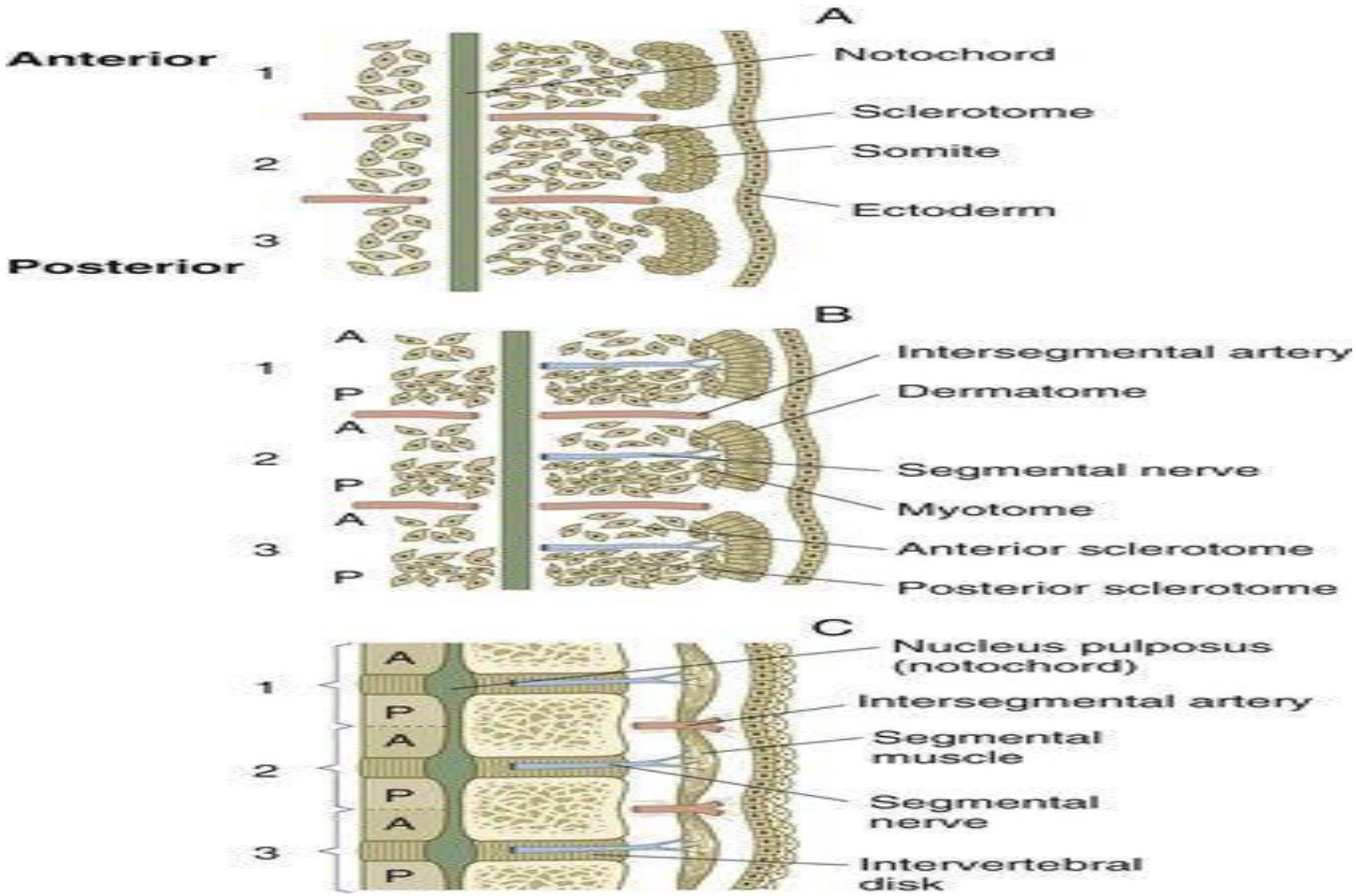


*Hox* gene expression in relation to the development of the vertebral column of the mouse.



# Organization of somites at earlier (**A**) and later (**B**) stages of development





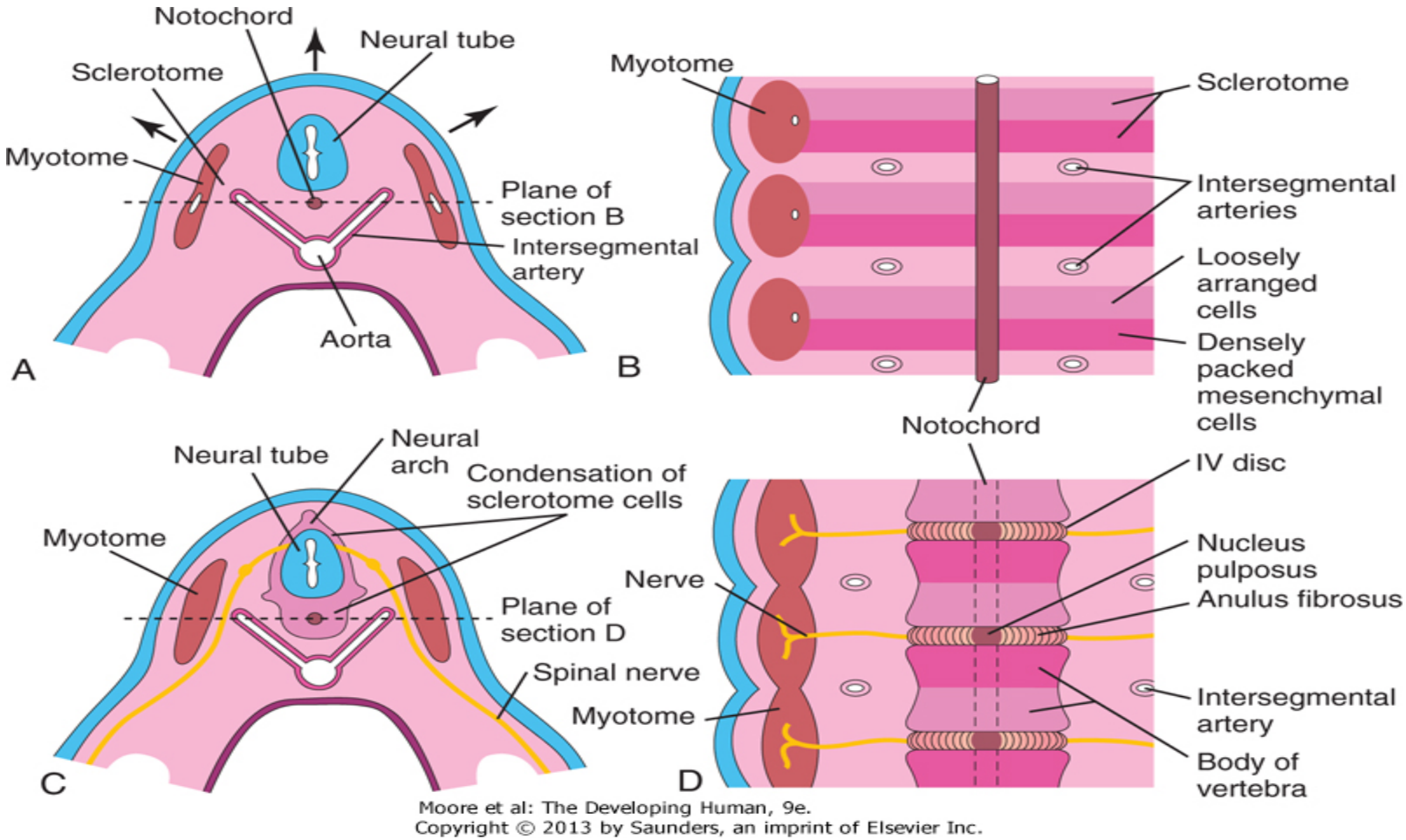

**A,** Early movement of seemingly homogeneous sclerotome from the somite. **B,** Breakup of the sclerotomal portions of the somites into anterior (A) and posterior (P) halves, and the coalescence of the posterior portion of one somite with the anterior portion of the one caudal to it to form the body of a vertebra. **C,** With this rearrangement, the segmental muscles (derived from the myotomes) extend across intervertebral joints and are supplied by spinal nerves that grow out between the anterior and posterior halves of the somites.

# DEVELOPMENT OF VERTEBRAL COLUMN

- During the precartilaginous or mesenchymal stage, mesenchymal cells from the sclerotomes are found in three main areas:
  - around the notochord
  - surrounding the neural tube
  - in the body wall
- Each sclerotome consists of loosely arranged cells cranially and densely packed cells caudally.

- Some densely packed cells move cranially, opposite the center of the myotome, where they form the intervertebral (IV) disc.
- The remaining densely packed cells fuse with the loosely arranged cells of the immediately caudal sclerotome to form the mesenchymal centrum, the primordium of the body of a vertebra - resegmentation.
- **Each centrum develops from two adjacent sclerotomes and becomes an intersegmental structure.**
- The nerves lie in close relationship to the IV discs, and the intersegmental arteries lie on each side of the vertebral bodies.
- In the thorax, the dorsal intersegmental arteries become the intercostal arteries.

- The notochord degenerates and disappears where it is surrounded by the developing vertebral bodies.
- Between the vertebrae, the notochord expands to form the gelatinous center of the IV disc-the nucleus pulposus .
- Nucleus is later surrounded by circularly arranged fibers that form the annulus fibrosus.
- **The nucleus pulposus and annulus fibrosus together form the IV disc.**
- The mesenchymal cells, surrounding the neural tube, form the neural arch, that is, the primordium of vertebral arch.
- The mesenchymal cells in the body wall form costal processes, which form the ribs in the thoracic region.




A, Transverse section through a 4-week embryo. The arrows indicate the dorsal growth of the neural tube and the simultaneous dorsolateral movement of the somite remnant, leaving behind a trail of sclerotomal cells. B, Diagrammatic frontal section of this embryo showing that the condensation of sclerotomal cells around the notochord consists of a cranial area of loosely packed cells and a caudal area of densely packed cells. C, Transverse section through a 5-week embryo showing the condensation of sclerotomal cells around the notochord and neural tube, which forms a mesenchymal vertebra. D, Diagrammatic frontal section illustrating that the vertebral body forms from the cranial and caudal halves of two successive sclerotomal masses. The intersegmental arteries now cross the bodies of the vertebrae, and the spinal nerves lie between the vertebrae. The notochord is degenerating except in the region of the intervertebral disc, where it forms the nucleus pulposus.

# CHORDOMA

- Remnants of the notochord may persist and form a chordoma, a rare neoplasm (tumor).
- Approximately one third of these slow-growing malignant tumors occur at the base of the cranium and extend to the nasopharynx.
- Chordomas infiltrate bone and are difficult to remove.
- Chordomas also develop in the lumbosacral region.
- Surgical resection has provided long-term disease-free survival for many patients.

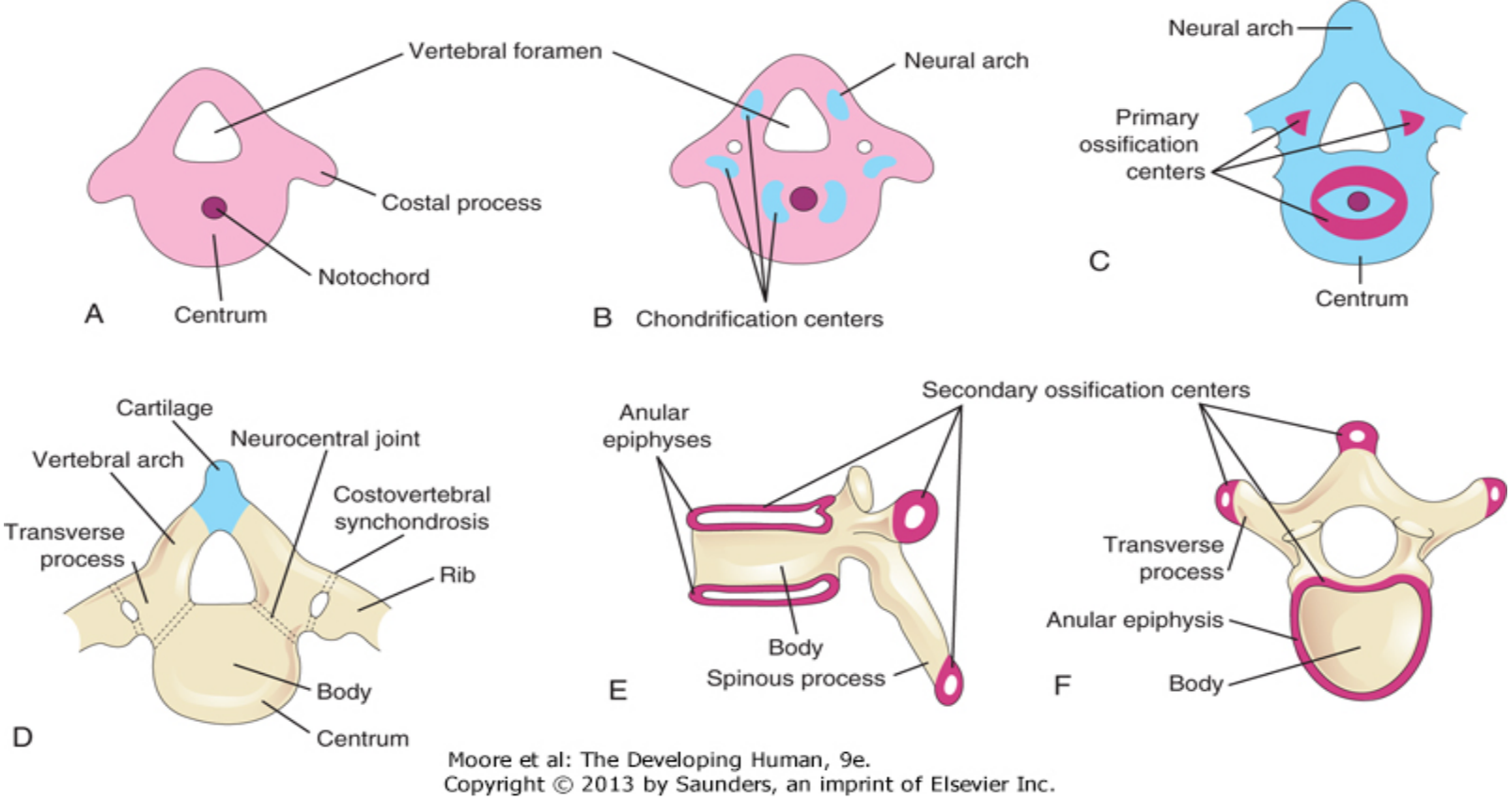
# CARTILAGINOUS STAGE OF VERTEBRAL DEVELOPMENT

- During the 6$^{th}$ week, chondrification centers appear in each mesenchymal vertebra.
- The two centers in each centrum fuse at the end of the embryonic period to form a cartilaginous centrum.
- Concomitantly, the centers in the neural arches fuse with each other and the centrum.
- The spinous and transverse processes develop from extensions of chondrification centers in the neural arch.
- Chondrification spreads until a cartilaginous vertebral column is formed.

# BONY STAGE OF VERTEBRAL DEVELOPMENT

- Ossification of typical vertebrae begins during the $7^{th}$ week and ends by the $25^{th}$ year.
- There are two primary ossification centers for the centrum:
  - ventral
  - dorsal
- These centers soon fuse to form one center.
- Three primary centers are present by the $8^{th}$ week:
  - one in the centrum
  - one in each half of the neural arch

- Each typical vertebra consists of three bony parts connected by cartilage:
  - a vertebral arch,
  - a body,
  - transverse processes
- The bony halves of the vertebral arch usually fuse during the first **3 to 5 years**.
- The arches first unite in the lumbar region, and union progresses cranially.




Stages of vertebral development. A, Mesenchymal vertebra at 5 weeks. B, Chondrification centers in a mesenchymal vertebra at 6 weeks. The neural arch is the primordium of the vertebral arch. C, Primary ossification centers in a cartilaginous vertebra at 7 weeks. D, Thoracic vertebra at birth consisting of three bony parts: vertebral arch, body of vertebra and transverse processes. Note the cartilage between the halves of the vertebral arch and between the arch and the centrum (neurocentral joint). E and F, Two views of a typical thoracic vertebra at puberty showing the location of the secondary centers of ossification.

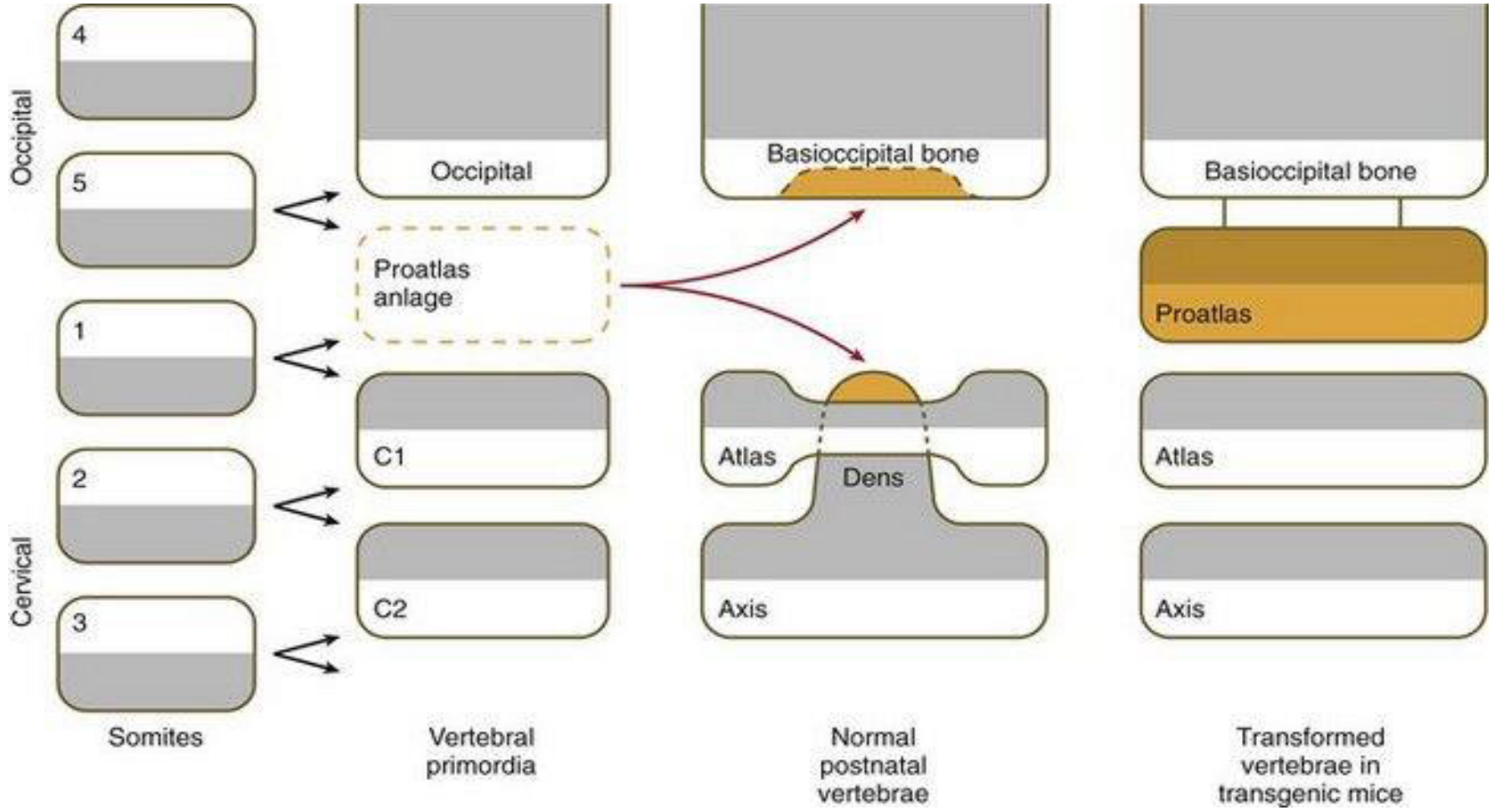
- The vertebral arch articulates with the centrum at cartilaginous neurocentral joints, which permit the vertebral arches to grow as the spinal cord enlarges.
- These joints disappear when the vertebral arch fuses with the centrum during the 3$^{rd}$ to 5$^{th}$ years.
- Five secondary ossification centers appear in the vertebrae after puberty:
  - One for the tip of the spinous process (1)
  - One for the tip of each transverse process (2)
  - Two anular epiphyses, one on the superior and one on the inferior rim of the vertebral body (2)

- The vertebral body is a composite of the anular epiphyses and the mass of bone between them.
- The vertebral body includes the centrum, parts of the vertebral arch, and the facets for the heads of the ribs.
- All secondary centers unite with the rest of the vertebrae at approximately **25 years of age**.
- Exceptions to the typical ossification of vertebrae occur in the atlas or C1 vertebra, axis or C2 vertebra, C7 vertebra, lumbar vertebrae, sacrum, and coccyx.

# ATLAS AND AXIS

- Among the vertebrae, the axis and atlas have an unusual morphology and a distinctive origin.
- The centrum of the atlas is deficient, but the area of the centrum is penetrated by the protruding **odontoid process** of the axis.
- The odontoid process consists of three fused centra that are presumably equivalent:
  - a half-segment from the centrum of a transitional bone (the **proatlas**) not found in humans,
  - the centrum that should have belonged to the atlas, and
  - the normal centrum of the axis
- This arrangement permits a greater rotation of the head about the cervical spine.

Formation of the atlas and axis in normal and transgenic mice. In normal development, cells from a proatlas anlage contribute to the formation of the basioccipital bone and the dens of the axis. The normal atlas forms an anterior arch (only a transient structure in other vertebrae) instead of a centrum. The cells that would normally form the centrum at the level of the atlas instead fuse with the axis to form the dens of the axis. In mice containing the *Hoxa7* (A7) transgene, a proatlas forms, and the atlas and axis have the form of typical vertebrae *(right column).*



# CONGENITAL ANOMALIES

- **The Notch signaling pathways are involved in the patterning of the vertebral column.**
- Severe congenital birth defects, including: VACTERL Syndrome (Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, and Limb birth defects), and CHARGE Association (coloboma of eye, heart defects: tetralogy of Fallot, patent ductus arteriosus, ventricular or atrial septal defect) are associated with mutation in Notch pathway genes.
- Minor defects of the vertebrae are common, but usually they are of little clinical importance.

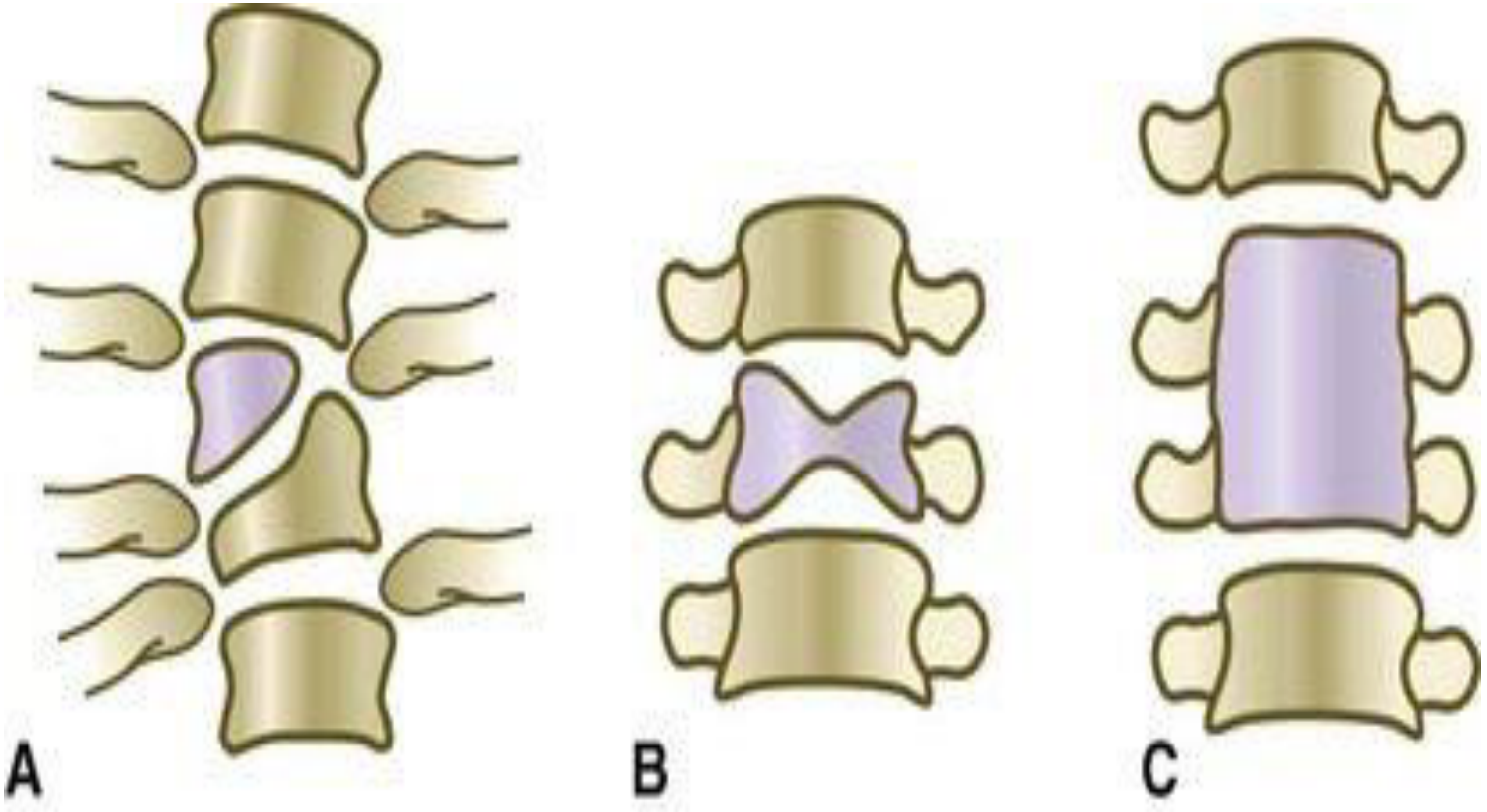
# VARIATION IN THE NUMBER OF VERTEBRAE

- Most people have 7 cervical, 12 thoracic, 5 lumbar, and 5 sacral vertebrae.
- A few have one or two additional vertebrae or one fewer.
- To determine the number of vertebrae, it is necessary to examine the entire vertebral column because an apparent extra (or absent) vertebra in one segment of the column may be compensated for by an absent (or extra) vertebra in an adjacent segment; for example, 11 thoracic-type vertebrae with 6 lumbar-type vertebrae.

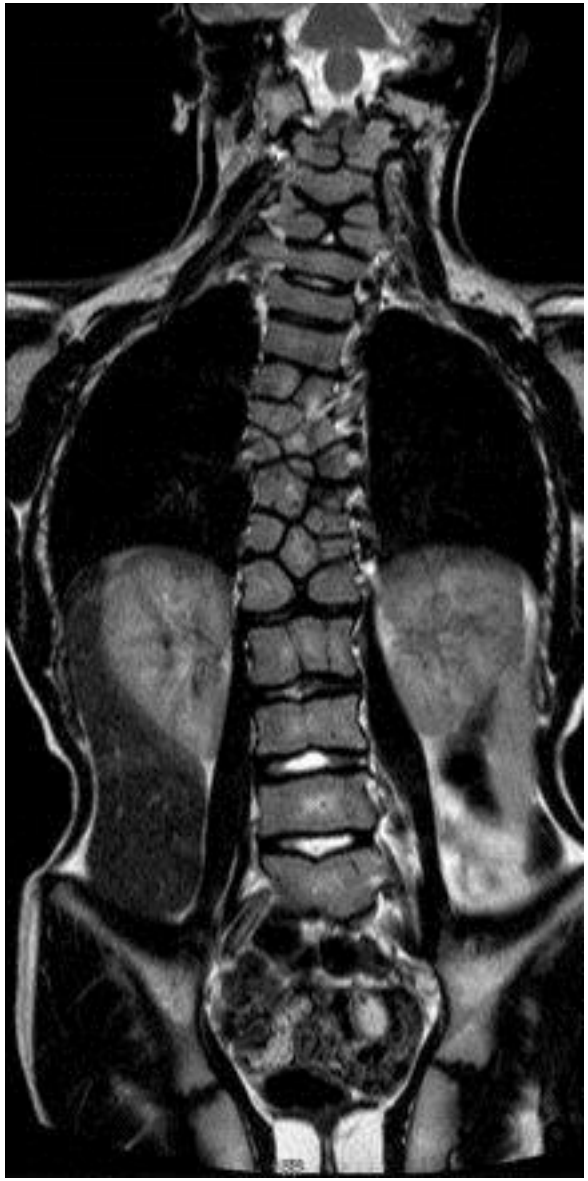
# ANOMALIES INVOLVING VERTEBRAL SEGMENTATION

- Certain conditions are characterized by abnormal segmentation of the vertebrae.
- A striking example is **spondylocostal dysostosis 2**, which is characterized by the presence of multiple ossified fragments (resulting from incomplete fusion of right and left sclerotome pairs) of vertebral centra in the thoracic region.
- The genetic defect in this condition is a homozygous mutant in the *MESP2* gene.
- This is the gene that, early in development, marks the position of a future somite (see Fig. 6.9).
- Other segmentation anomalies take the form of:
  - isolated bony wedges (**hemivertebrae**),
  - sagittally cleft vertebrae (**butterfly vertebrae**)
  - or fused vertebrae (**block vertebrae)**
- Hemivertebrae, a common cause of congenital **scoliosis** (lateral curvature of the vertebral column), are sometimes related to mutations of genes associated with the segmentation clock mechanism (e.g., *lunatic fringe*, *MESP2*, the Notch ligand *DLL3*) that produces the somites.
- Butterfly vertebrae are thought to result from a midline fusion defect that reduces the connection between the right and left sclerotomes.

# Common segmental abnormalities of vertebrae (indicated in *purple*): A-Hemivertebrae, B-Butterfly, C-Block vertebrae

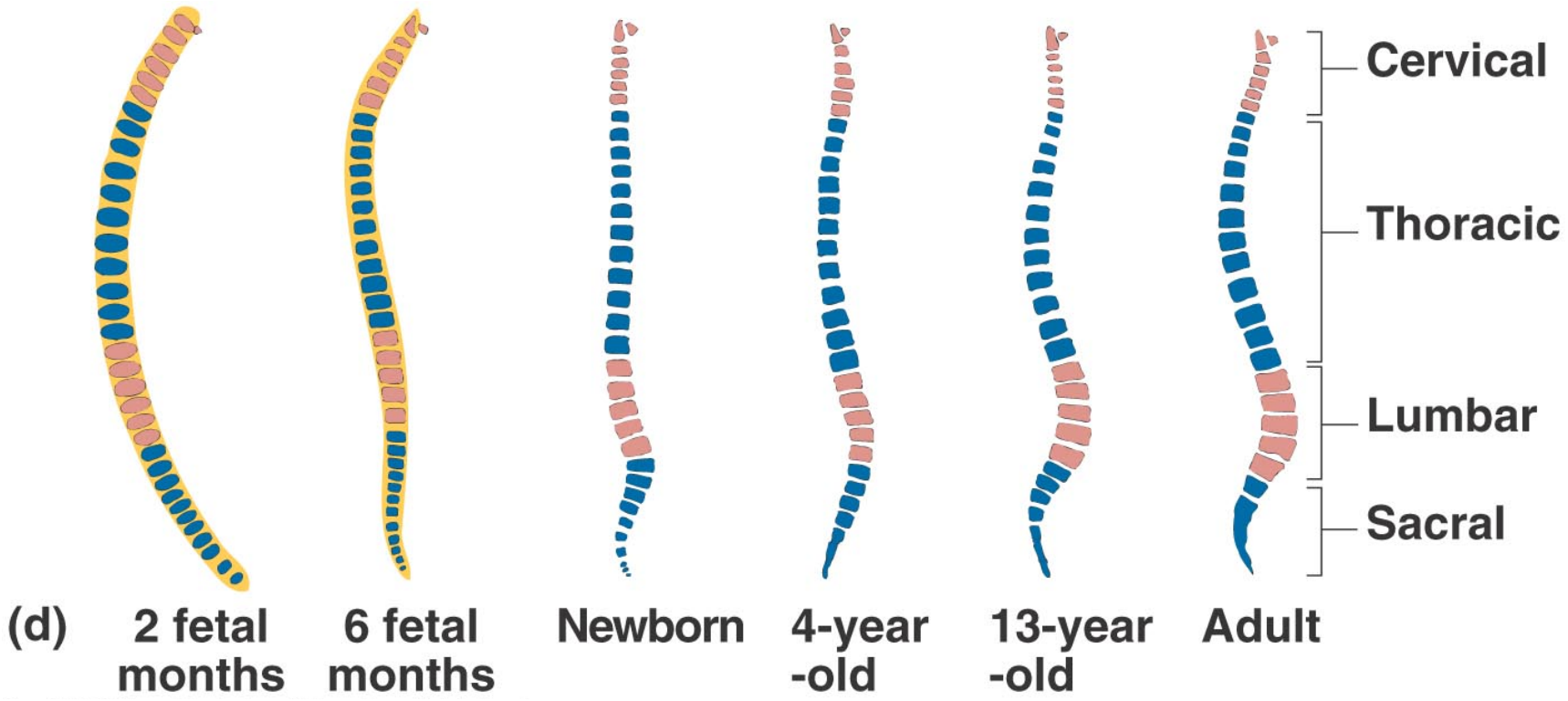


Magnetic resonance imaging scan of the spine of an individual with spondylocostal dysostosis resulting from a homozygous mutation of ***MESP-2.*** In this individual, highly abnormal segmentation is seen in the thoracic vertebrae.

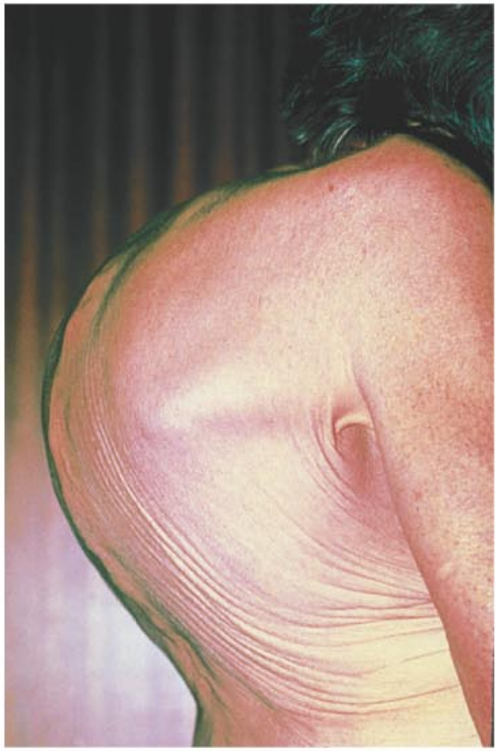


- When standing, body weight must be transmitted through the column to the hips and lower limbs.
- But most of the body weight lies in front of the column - various curves bring the weight of the body in line with the body axis and its center of gravity.
- Two primary curves:
  - Thoracic
  - Sacral
- Secondary curves:
  - Cervical
  - Lumbar

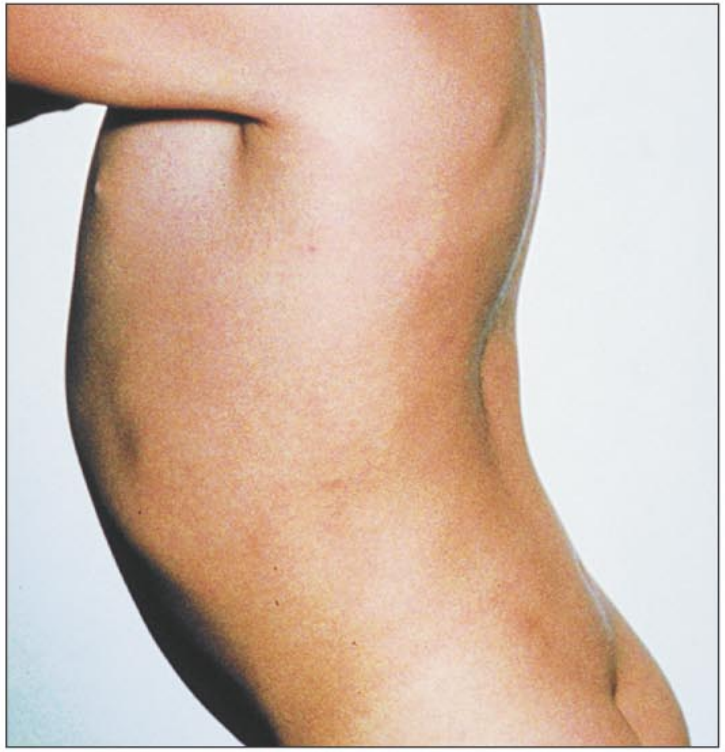
# DEVELOPMENT OF SPINAL CURVES



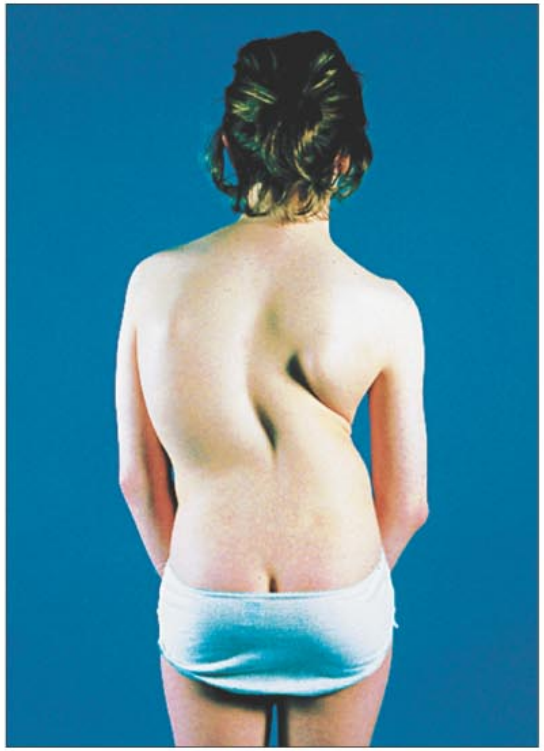
# Abnormal curvatures



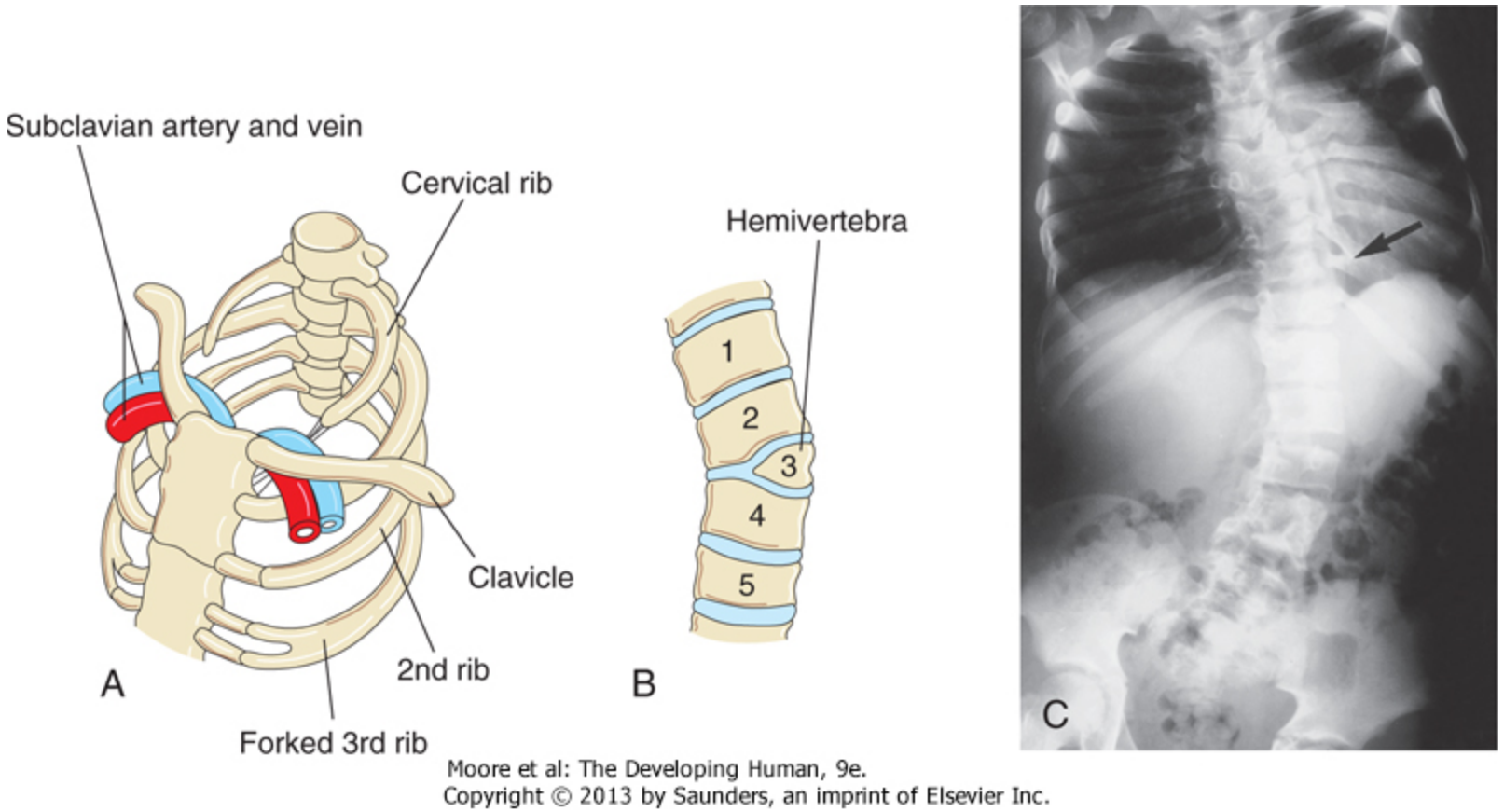
(a) Kyphosis



(b) Lordosis



(c) Scoliosis




Moore et al: The Developing Human, 9e.


Vertebral and rib abnormalities. A, Cervical and forked ribs. Observe that the left cervical rib has a fibrous band that passes posterior to the subclavian vessels and attaches to the manubrium of the sternum. B, Anterior view of the vertebral column showing a hemivertebra. The right half of the third thoracic vertebra is absent. Note the associated lateral curvature (scoliosis) of the vertebral column. C, Radiograph of a child with the kyphoscoliotic deformity of the lumbar region of the vertebral column showing multiple anomalies of the vertebrae and ribs. Note the fused ribs (arrow).

# DEVELOPMENT OF RIBS

- The ribs develop from the mesenchymal costal processes of the thoracic vertebrae.
- They become cartilaginous during the embryonic period and ossify during the fetal period.
- The original site of union of the costal processes with the vertebra is replaced by costovertebral synovial joints.
- Seven pairs of ribs (1-7)-true ribs-attach through their own cartilages to the sternum.
- Three pairs of ribs (8-10)-false ribs-attach to the sternum through the cartilage of another rib or ribs.
- The last two pairs of ribs (11 and 12)-floating ribs-do not attach to the sternum.

- The ribs arise from zones of condensed mesenchymal cells lateral to the centrum.
- The proximal part of a rib (head, neck, and tubercle) arises from the central sclerotome.
- Because of the resegmentation of the somites as they form the vertebrae, the distal part (shaft) of the rib is derived from the lateral part of the adjacent cranial somite.
- By the time ossification in the vertebrae begins, the ribs separate from the vertebrae.

# ACCESSORY RIBS

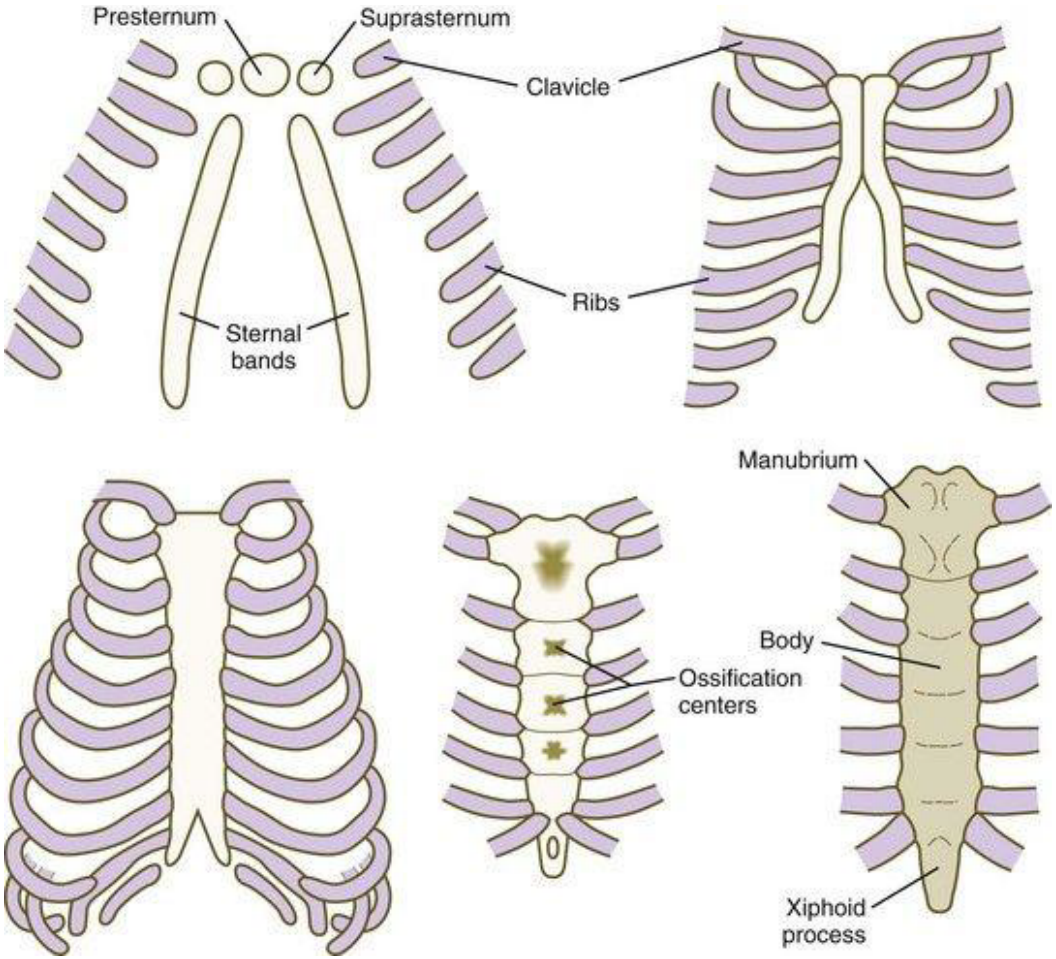
- Accessory ribs, usually rudimentary, result from the development of the costal processes of cervical or lumbar vertebrae.
- These processes usually form ribs only in the thoracic region.
- The most common type of accessory rib is a lumbar rib, but it usually does not cause problems.
- A cervical rib occurs in 0.5% to 1% of individuals - usually attached to the manubrium of the sternum, or the seventh cervical vertebra.

- Accessory ribs may be unilateral or bilateral.
- Pressure of a cervical rib on the brachial plexus of nerves, located partly in the neck and axilla, or on the subclavian artery often produces neurovascular symptoms (e.g., paralysis and anesthesia of the upper limb).
- **FUSED RIBS**
  - Fusion of ribs occasionally occurs posteriorly when two or more ribs arise from a single vertebra.
  - Fused ribs are often associated with a hemivertebra.

# DEVELOPMENT OF STERNUM

- A pair of vertical mesenchymal bands, sternal bars, develop ventrolaterally in the body wall.
- The **sternum**, which along with the connective tissue surrounding the distal ribs is derived from lateral plate mesoderm, arises as a pair of cartilaginous bands that converge at the ventral midline as the ventral body wall consolidates.
- Chondrification occurs in these bars as they move medially.
- By 10 weeks, they fuse craniocaudally in the median plane to form cartilaginous models of the manubrium, sternebrae (segments of sternal body), and xiphoid process.
- Centers of ossification appear craniocaudally in the sternum before birth, except that for the xiphoid process, which appears during childhood.

# Successive stages in the development of the sternum and clavicle



# ANOMALIES OF STERNUM

- A concave depression of the lower sternum-pectus excavatum-is the most common (90%) thoracic wall defect seen.
- Males are more often affected (1:400-1:1000 live births). It is probably due to overgrowth of the costal cartilages, which displaces the lower sternum inward.
- Minor sternal clefts (e.g., a notch or foramen in the xiphoid process) are common and are of no clinical concern.
- A sternal foramen of varying size and form occurs occasionally at the junction of the third and fourth sternebrae (segments of primordial sternum).
- This insignificant foramen is the result of incomplete fusion of the cartilaginous sternal bars during the embryonic period.

# DEVELOPMENT OF CRANIUM

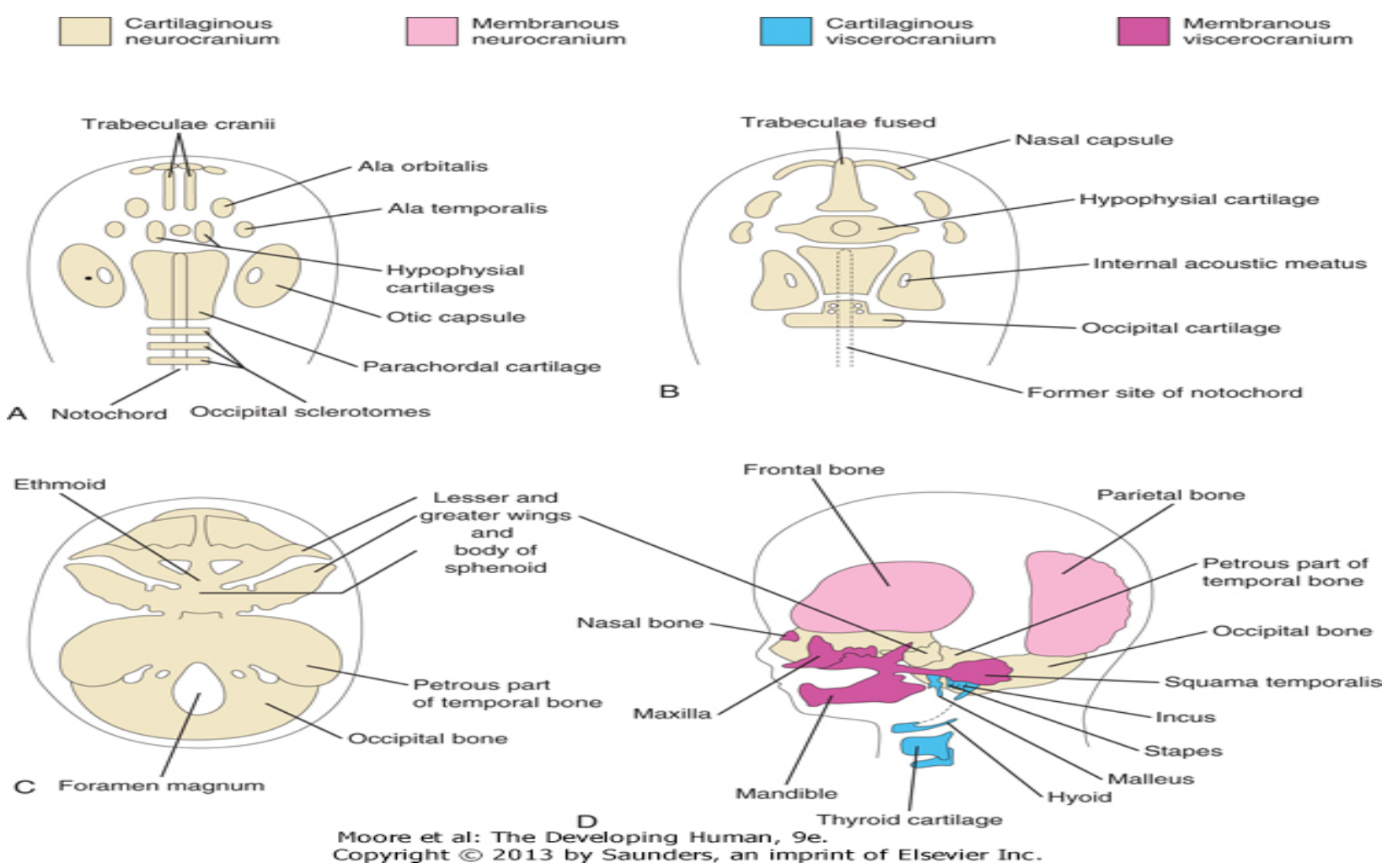
- The cranium (skull) develops from mesenchyme around the developing brain.
- The growth of the neurocranium (bones of cranium enclosing the brain) is initiated from ossification centers within the desmocranium mesenchyme, which is the primordium of the cranium.
- Transforming growth factors beta (TGF-β) plays a critical role in the development of the cranium by regulating osteoblast differentiation.
- The cranium consists of the:
  - Neurocranium, the bones of the cranium enclosing the brain (brain box)
  - Viscerocranium, the bones of the facial skeleton derived from the pharyngeal arches

# CARTILAGINOUS NEUROCRANIUM

- Initially, the cartilaginous neurocranium or chondrocranium consists of the cartilaginous base of the developing cranium, which forms by fusion of several cartilages.
- Later, endochondral ossification of the chondrocranium forms the bones in the base of the cranium.
- The ossification pattern of these bones has a definite sequence, beginning with the occipital bone, body of sphenoid, and ethmoid bone.

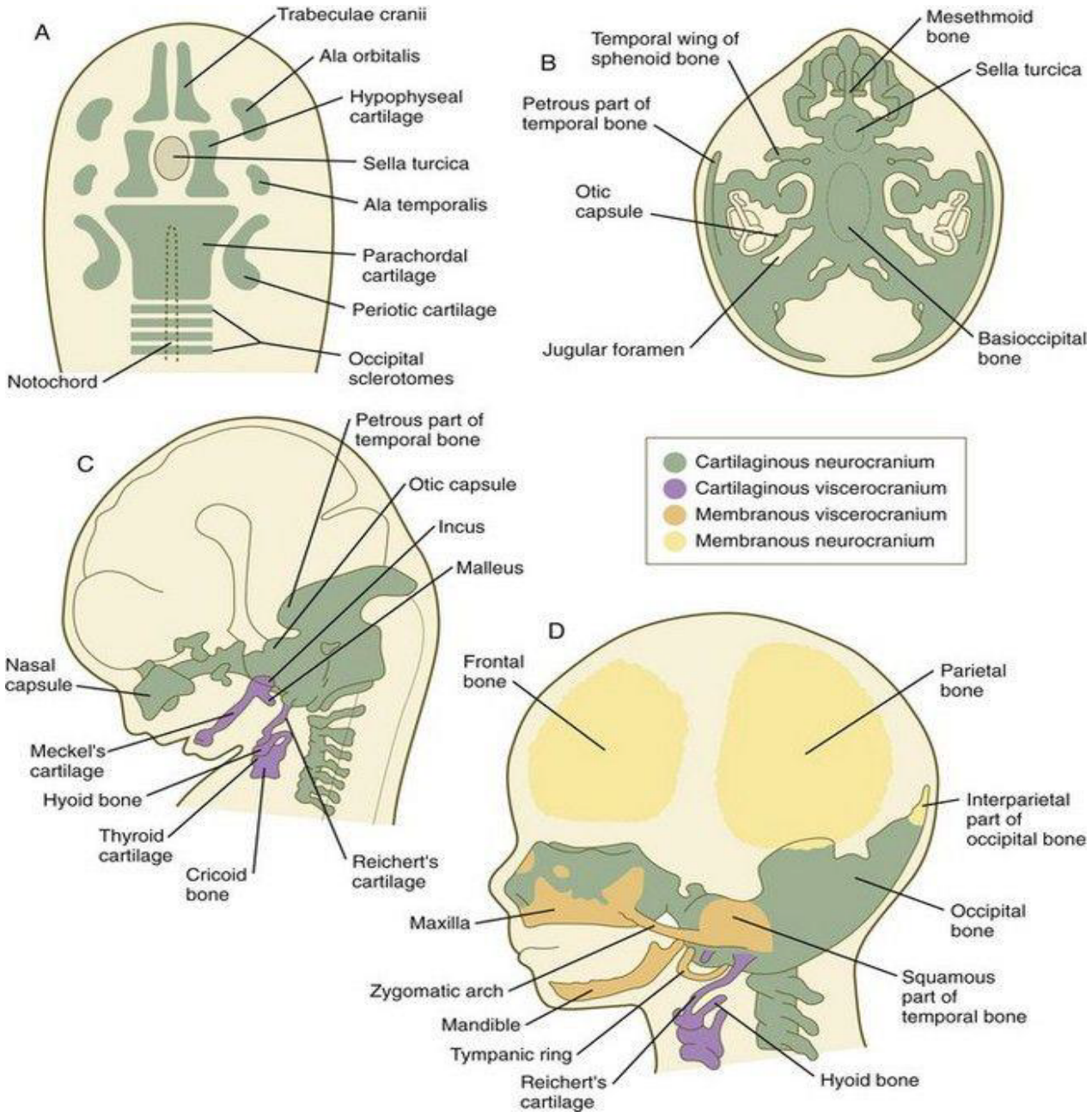
- The parachordal cartilage, or basal plate, forms around the cranial end of the notochord, and fuses with the cartilages derived from the sclerotome regions of the occipital somites.
- This cartilaginous mass contributes to the base of the occipital bone; later, extensions grow around the cranial end of the spinal cord and form the boundaries of the foramen magnum.

- The **hypophysial cartilage** forms around the developing pituitary gland (hypophysis cerebri) and fuses to form the body of the sphenoid bone.
- The **trabeculae cranii** fuse to form the body of the ethmoid bone, and the **ala orbitalis** forms the lesser wing of the sphenoid bone.
- **Otic capsules** develop around the otic vesicles, the primordia of the internal ears, and form the petrous and mastoid parts of the temporal bone.
- **Nasal capsules** develop around the nasal sacs and contribute to the formation of the ethmoid bone.

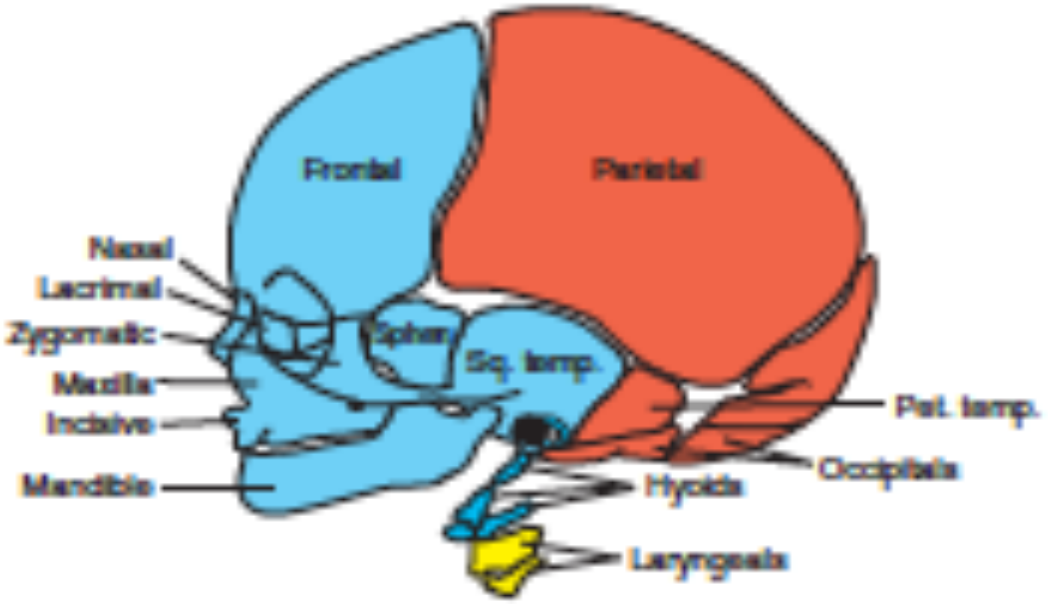


Moore et al: The Developing Human, 9e.


Stages in the development of the cranium. A to C, Views of the base of the developing cranium (viewed superiorly). D, A lateral view. A, At 6 weeks showing the various cartilages that will fuse to form the chondrocranium. B, At 7 weeks, after fusion of some of the paired cartilages. C, At 12 weeks showing the cartilaginous base of the cranium formed by the fusion of various cartilages. D, At 20 weeks indicating the derivation of the bones of the fetal cranium.




Origins and development of the major skull bones

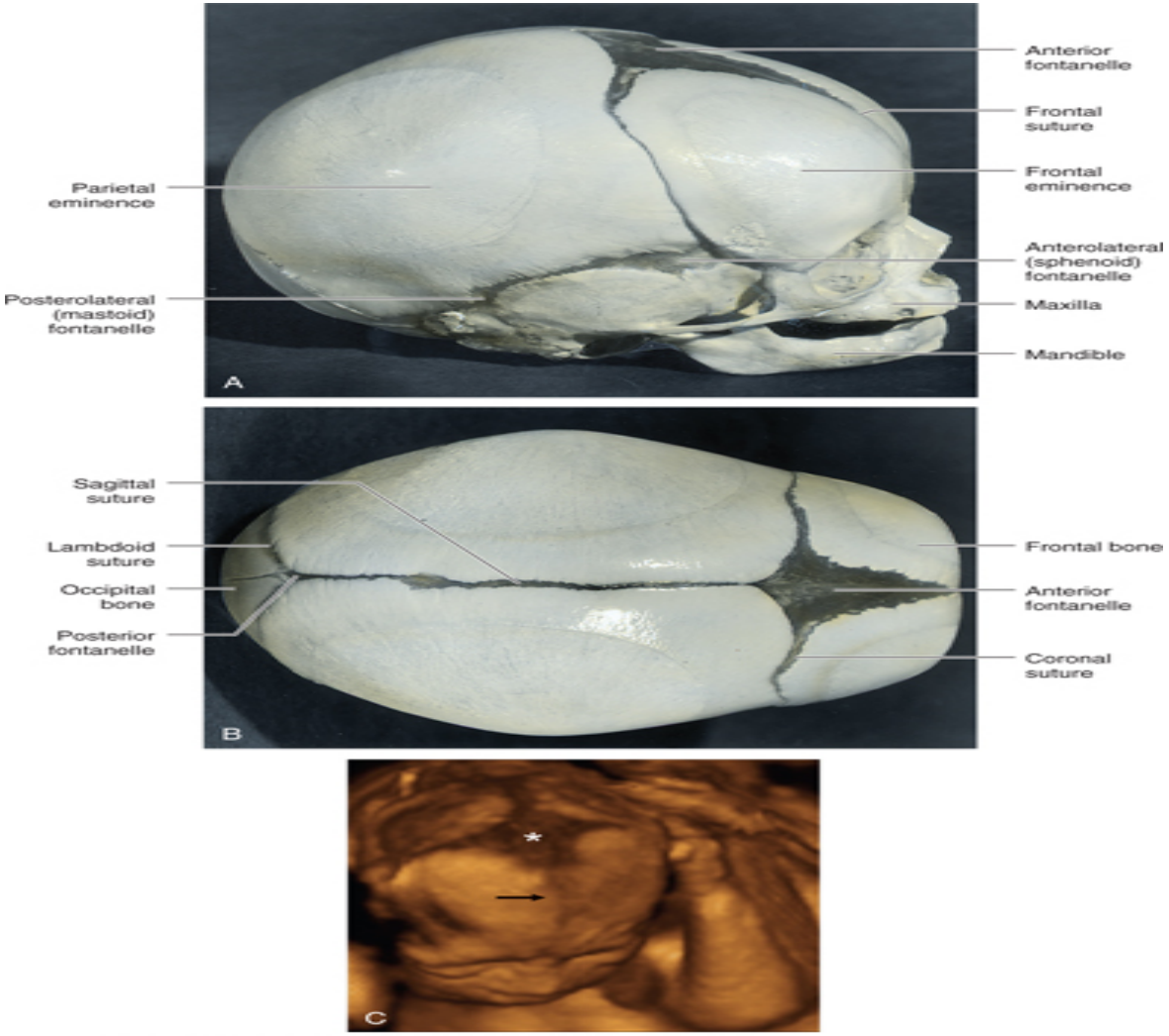



Skeletal structures of the head and face. Mesenchyme for these structures is derived from neural crest (blue), paraxial mesoderm (somites and somitomeres) (red), and lateral plate mesoderm (yellow).

# MEMBRANOUS NEUROCRANIUM

- Membranous ossification (intramembranous ossification) occurs in the head mesenchyme at the sides and top of the brain, forming the calvaria (skullcap).
- During fetal life, the flat bones of the calvaria are separated by dense connective tissue membranes that form fibrous joints, the sutures of the calvaria.

- Six large fibrous areas-fontanelles-are present where several sutures meet.
- The softness of the bones and their loose connections at the sutures enable the calvaria to undergo changes of shape during birth - molding.
- During molding of the fetal cranium (adaptation of the fetus's head to the pelvic cavity during birth), the frontal bones become flat, the occipital bone is drawn out, and one parietal bone slightly overrides the other one.
- Within a few days after birth, the shape of the calvaria returns to normal.




Moore et al: The Developing Human, 9e.


A fetal cranium showing the bones, fontanelles, and sutures. A, Lateral view. B, Superior view. The posterior and anterolateral fontanelles disappear because of growth of surrounding bones, within 2 or 3 months after birth, but they remain as sutures for several years. The posterolateral fontanelles disappear in a similar manner by the end of the first year and the anterior fontanelle by the end of the second year. The halves of the frontal bone normally begin to fuse during the second year, and the frontal suture is usually obliterated by the eighth year. The other sutures disappear during adult life, but the times when the sutures close are subject to wide variations. C, Three-dimensional ultrasound rendering of the fetal head at 22 weeks. Note the anterior fontanelle (*) and the frontal suture (arrow). The coronal and sagittal sutures are also shown.

# CARTILAGINOUS VISCEROCRANIUM

- Most mesenchyme in the head region is derived from the neural crest.
- Neural crest cells migrate into the pharyngeal arches and form the bones and connective tissue of craniofacial structures.
- Homeobox (Hox) genes regulate the migration and subsequent differentiation of the neural crest cells, which are crucial for the complex patterning of the head and face.
- These parts of the fetal cranium are derived from the cartilaginous skeleton of the first two pairs of pharyngeal arches .

# MEMBRANOUS VISCEROCRANIUM

- Membranous ossification occurs in the maxillary prominence of the first pharyngeal arch, and subsequently forms the squamous temporal, maxillary, and zygomatic bones.
- The squamous temporal bones become part of the neurocranium.
- The mesenchyme in the mandibular prominence of the first pharyngeal arch condenses around its cartilage and undergoes membranous ossification to form the mandible.
- Some endochondral ossification occurs in the median plane of the chin and the mandibular condyle.

# CRANIUM OF NEONATE

- After recovering from molding, the neonate's cranium is rather round and its bones are thin.
- Like the fetal cranium, it is large in proportion to the rest of the skeleton, and the face is relatively small compared with the calvaria.
- The small facial region of the cranium results from the small size of the jaws, virtual absence of paranasal (air) sinuses, and underdevelopment of the facial bones.

# POSTNATAL GROWTH OF CRANIUM

- The fibrous sutures of the neonate's calvaria permit the brain to enlarge during infancy and childhood.
- Greatest growth - first 2 years.
- Capacity increase till 16 years of age.
- Further increase in size due to:
  - thickening of its bones - 3 to 4 years
  - face and jaws changes, coincide with eruption of the primary (deciduous) teeth
- Facial changes more marked after the secondary (permanent) teeth erupt and air sinuses form.
- Growth of these sinuses is important in altering the shape of the face and in adding resonance to the voice.

# KLIPPEL-FEIL SYNDROME (BREVICOLLIS)

- Main features of this syndrome are:
  - shortness of the neck,
  - low hairline,
  - restricted neck movements,
  - fusion of cervical vertebral bodies
  - abnormalities of the brainstem and cerebellum.
- Most cases, the number of cervical vertebral bodies is fewer than normal due to fusion of vertebrae before birth.
- Some cases, there is a lack of segmentation of several elements of the cervical region of the vertebral column.
- The number of cervical nerve roots may be normal but they are small, as are the intervertebral foramina.
- Individuals with this syndrome may have other birth defects, including scoliosis (abnormal lateral and rotational curvature of the vertebral column) and urinary tract disorders.

# SPINA BIFIDA

- Failure of the halves of the embryonic cartilaginous neural arch to fuse results in major birth defects-spina bifida.
- The incidence of these vertebral defects ranges from 0.04% to 0.15%;
- They occur more frequently in girls than boys.
- Most cases of spina bifida (80%) are "open" and covered by a thin membrane.

# HEMIVERTEBRA

- In normal circumstances, the developing vertebral bodies have two chondrification centers that soon unite.
- A hemivertebra results from failure of one of the chondrification centers to appear and subsequent failure of half of the vertebra to form.
- Hemivertebrae are the most common cause of congenital scoliosis (lateral and rotational curvature) of the vertebral column.
- There are other less common causes of scoliosis (e.g., myopathic scoliosis resulting from weakness of the back muscles).

# RACHISCHISIS

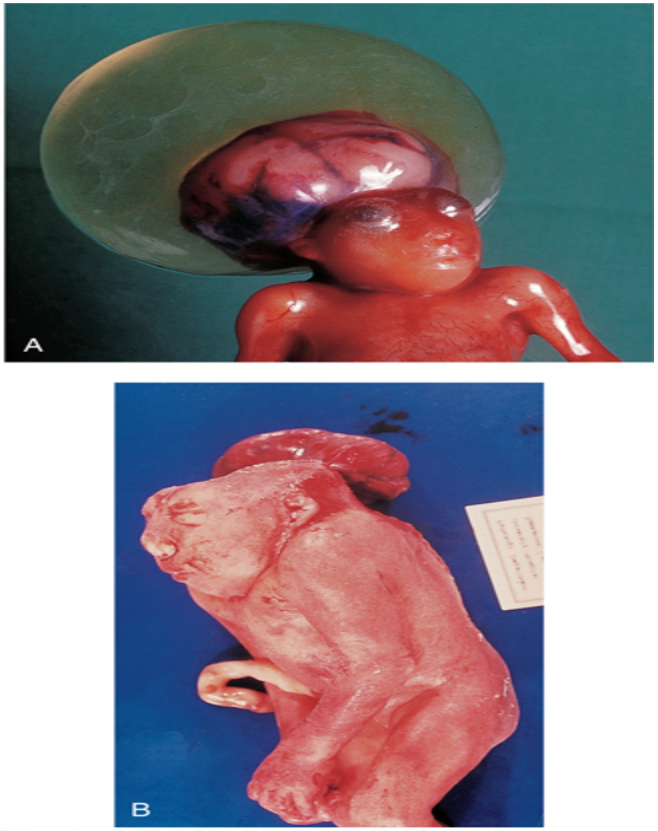
- Rachischisis (cleft vertebral column) refers to vertebral abnormalities in a complex group of anomalies (spinal dysraphism) that primarily affect axial structures.
- In these infants the neural folds fail to fuse, either because of faulty induction by the underlying notochord, or from the action of teratogenic agents on the neuroepithelial cells in the neural folds.
- The neural and vertebral defects may be extensive or be restricted to a small area.

# CRANIAL BIRTH DEFECTS

- These abnormalities range from major defects that are incompatible with life to those that are minor and insignificant.
- With large defects, there is often herniation of the meninges and/or brain.

# ACRANIA

- In this condition, there is complete or partial absence of the neurocranium (brain box); extensive defects of the vertebral column are often present.
- Acrania associated with meroencephaly (partial absence of the brain) occurs approximately once in 1000 births and is incompatible with life.
- Meroencephaly results from failure of the cranial end of the neural tube to close during the fourth week.
- This birth defect causes subsequent failure of the neurocranium to form.





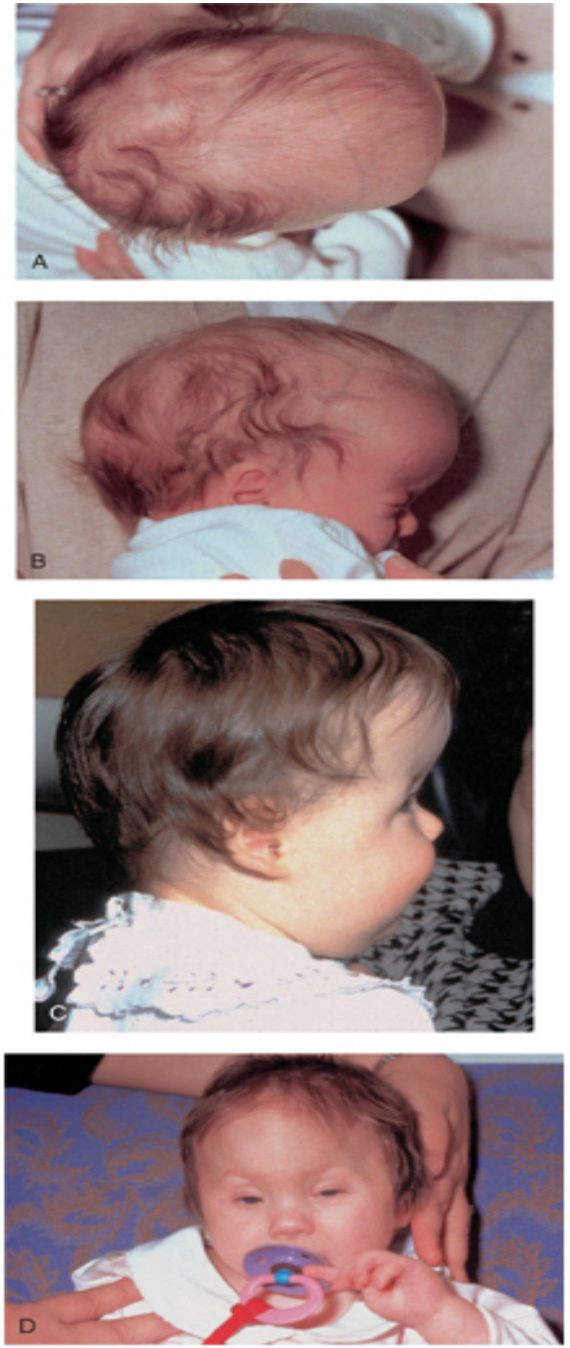
A, A second-trimester fetus with holoacrania (absence of the cranium, i.e., acrania). Note the cyst-like structure surrounding the intact fetal brain. B, Lateral view of a newborn infant with acrania and meroencephaly (partial absence of the brain), as well as rachischisis, which are extensive clefts in vertebral arches of the vertebral column (not clearly visible).

# CRANIOSYNOSTOSIS

- Prenatal fusion of the cranial sutures results in several birth defects.
- The cause of craniosynostosis is unclear.
- Homeobox gene Msx2, Alx4, FGFR, TWIST, and MSX2 mutations have been implicated in the molecular mechanisms of craniosynostosis and other cranial defects.
- A strong association between maternal anticonvulsant use during early pregnancy and infant craniosynostosis has been reported.
- These birth defects are more common in males than in females and they are often associated with other skeletal anomalies.

- The type of deformed cranium produced depends on which sutures close prematurely.
- If the sagittal suture closes early, the cranium becomes long, narrow, and wedge shaped-**scaphocephaly** - about half the cases of craniosynostosis.
- Another 30% of cases involve premature closure of the coronal suture, which results in a high, tower-like cranium-**brachycephaly**.
- If the coronal suture closes prematurely on one side only, the cranium is twisted and asymmetrical-**plagiocephaly**.
- Premature closure of the frontal (metopic) suture results in a deformity of the frontal bone and other anomalies-**trigonocephaly**.

Craniosynostosis. A and B, An infant with scaphocephaly. This condition results from premature closure (synostosis) of the sagittal suture. Note the elongated, wedge-shaped cranium seen from above (A) and the side (B). C, An infant with bilateral premature closure of the coronal suture (brachycephaly). Note the high, markedly elevated forehead. D, An infant with premature closure of the frontal suture (trigonocephaly). Note the hypertelorism (abnormal distance between the eyes) and prominent midline ridging of the forehead.



# MICROCEPHALY

- Infants with this birth defect are born with a normal sized or slightly small calvaria.
- The fontanelles close during early infancy and the other sutures close during the first year.
- However, this defect is not caused by premature closure of sutures.
- Microcephaly is the result of abnormal development of the central nervous system in which the brain, and consequently the neurocranium, fail to grow.
- Generally, infants with microcephaly have small heads and are mentally deficient.

# ANOMALIES AT CRANIOVERTEBRAL JUNCTION

- Congenital abnormalities at the craniovertebral junction are present in approximately 1% of neonates, but they may not produce symptoms until adult life.
- The following are examples of these anomalies:
  - basilar invagination (superior displacement of bone around the foramen magnum),
  - assimilation of the atlas (nonsegmentation at the junction of the atlas and occipital bone),
  - atlantoaxial dislocation,
  - Arnold-Chiari malformation,
  - separate dens (failure of the centers in the dens to fuse with the centrum of the axis)

# DEVELOPMENT OF APPENDICULAR SKELETON

- The appendicular skeleton consists of:
  - the pectoral girdle
  - pelvic girdle
  - the limb bones
- Mesenchymal bones form during the 5$^{th}$ week as condensations of mesenchyme appear in the limb buds.
- During the 6$^{th}$ week, the mesenchymal bone models in the limbs undergo chondrification to form hyaline cartilage bone models.

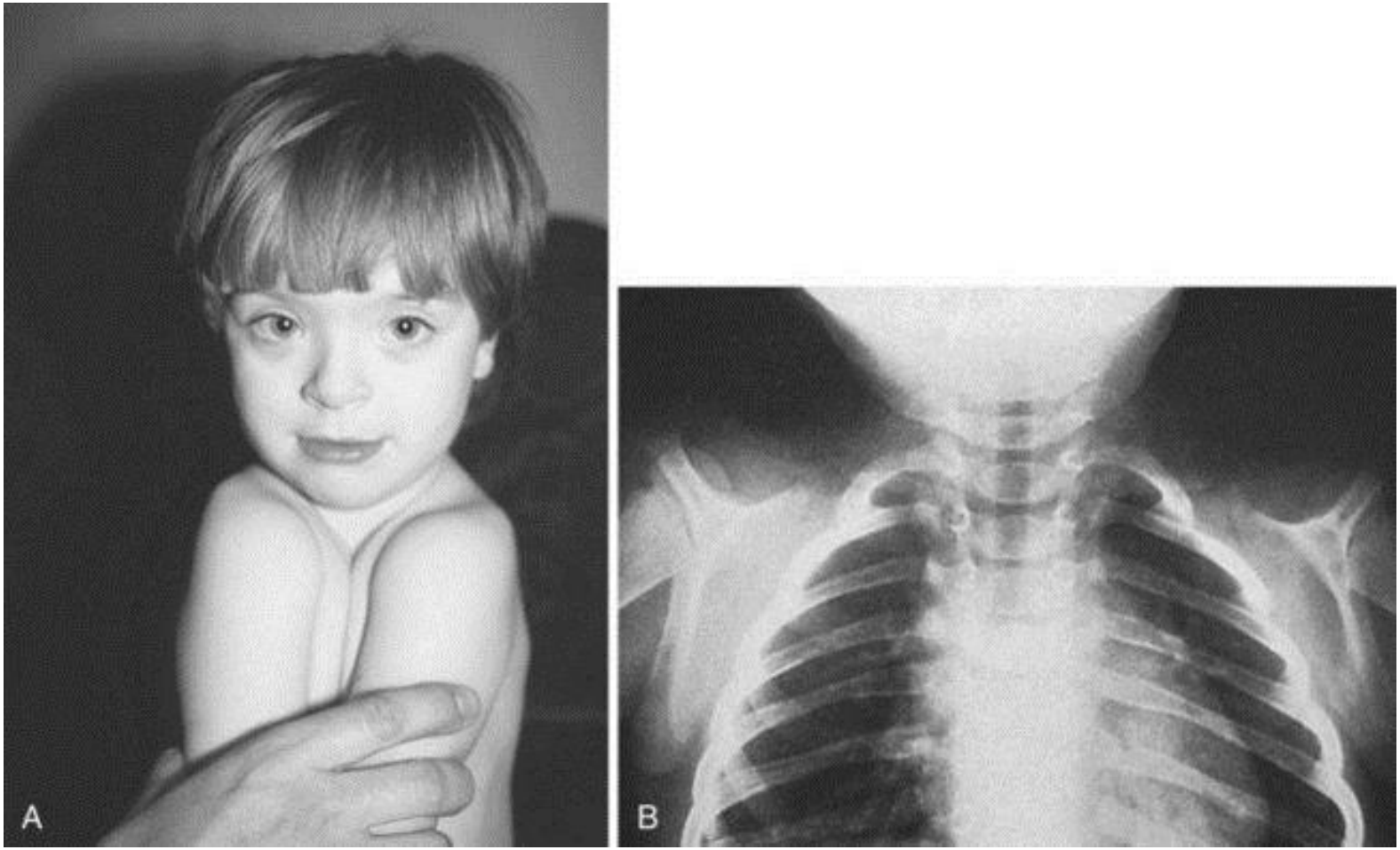
# CLAVICLE

- **Clavicle** initially develops by membranous ossification and it later forms growth cartilages at both ends.
- Clavicles ossification appear before any other bones in the body.
- Pectoral girdle and upper limb bones appear slightly before those of the pelvic girdle and lower limb bones.
- Virtually all primary centers of ossification are present at birth.

- The clavicle is considered a long bone, as it has a medullary cavity and an epiphysis at either end to permit growth.
- The clavicle is the first fetal bone to undergo primary ossification, and its medial epiphysis is the last to fuse.
- However, whereas other long bones undergo initial endochondral ossification, the clavicle ossifies via intramembranous ossification with no prior endochondral ossification.
- The two primary ossification centers appear by the 6th week intrauterine and fuse together about one week later.
- After the osteoid matrix is laid down, cartilage appears at the acromial and sternal ends of the bone, at which point growth becomes a combination of endochondral and membranous ossification.

- The medial cartilaginous mass contributes more to clavicular growth in length than does the lateral mass, perhaps as much as 80% of the bone length.
- The combination of the spatial location of the two ossification centers at either end of the bone and endochondral ossification at these sites gives the clavicle its unique s-shape by 8-9 prenatal weeks.
- The bone attains its adult form by 11 prenatal weeks.
- Growth slows after birth until the growth spurt between 5 and 7 years, then slows again until the pubertal growth spurt.

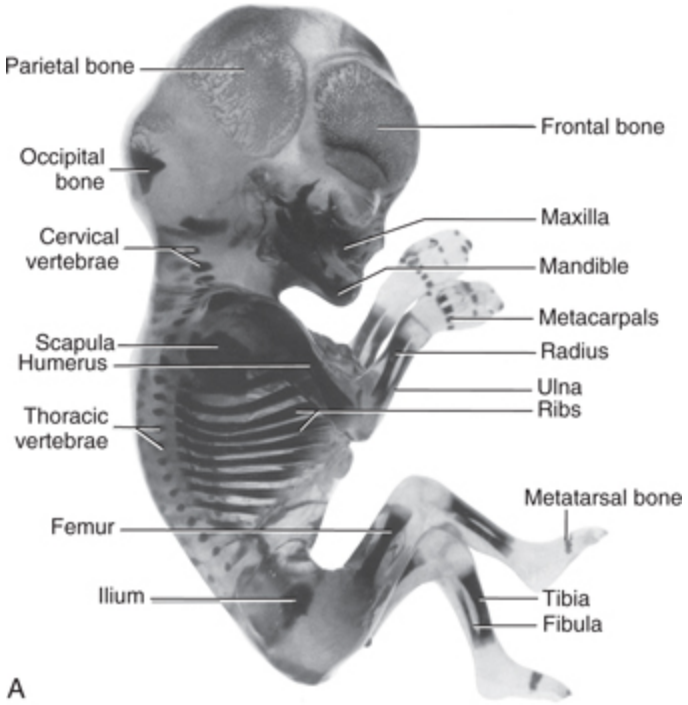
# Cleidocranial dysplasia



# LIMBS

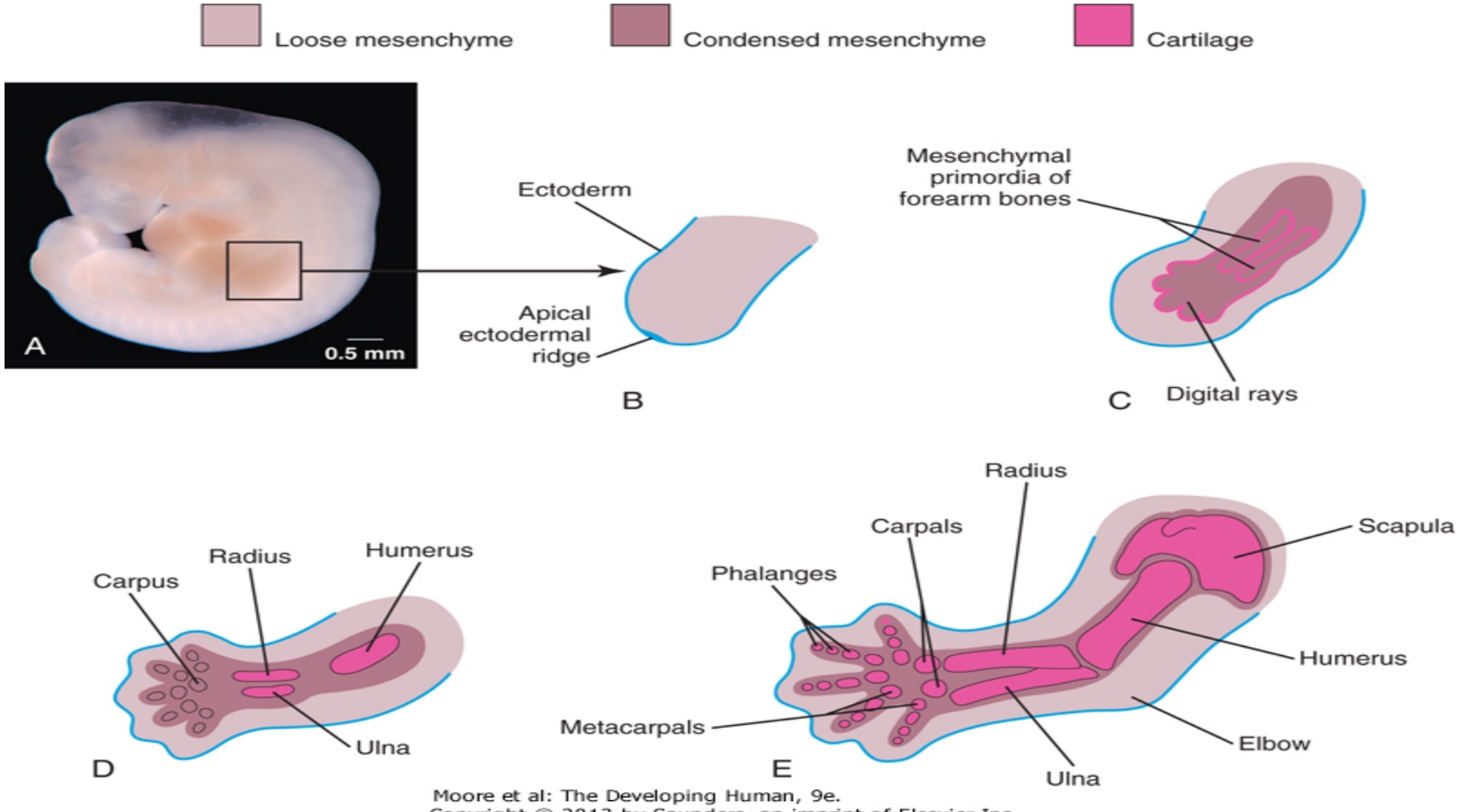
- The secondary ossification centers of the bones at the knee are the first to appear in utero.
- The centers for the distal end of the femur and the proximal end of the tibia usually appear during the last month of intrauterine life.
- Consequently, these centers are usually present at birth; however, most secondary centers of ossification appear after birth.

Alizarin-stained and cleared human fetuses. A, A 12-week fetus. Observe the degree of progression of ossification from the primary centers of ossification, which is endochondral in the appendicular and axial parts of the skeleton except for most of the cranial bones (i.e., those that form the neurocranium). Observe that the carpus and tarsus are wholly cartilaginous at this stage, as are the epiphyses of all long bones. B and C, An approximately 20-week fetus.




# BONE AGE

- Bone age is a good index of general maturation.
- **How:** Determination of the number, size, and fusion of epiphysial centers from radiographs is a commonly used method.
- A radiologist determines the bone age of a person by assessing the ossification centers using two criteria:
  - The time of appearance of calcified material in the diaphysis and/or the epiphysis is specific for each diaphysis and epiphysis and for each bone and sex.
  - The disappearance of the dark line representing the epiphysial cartilage plate indicates that the epiphysis has fused with the diaphysis.
- Fusion of the diaphysial-epiphysial centers, which occurs at specific times for each epiphysis, happens 1 to 2 years earlier in females than in males.
- Individual variation also occurs.
- In the fetus, ultrasonography is used for the evaluation and measurement of bones as well as for determination of fertilization age.




A, Photograph of an embryo at approximately 28 days showing the early appearance of the limb buds. B, Longitudinal section through an upper limb bud showing the apical ectodermal ridge, which has an inductive influence on the mesenchyme in the limb bud. This ridge promotes growth of the mesenchyme and appears to give it the ability to form specific cartilaginous elements. C, Similar sketch of an upper limb bud at approximately 33 days showing the mesenchymal primordia of the forearm bones. The digital rays are mesenchymal condensations that undergo chondrification and ossification to form the bones of the hand. D, Upper limb at 6 weeks showing the cartilage models of the bones. E, Later in the sixth week showing the completed cartilaginous models of the bones of the upper limb.

- Thanatophoric dysplasia is the most common type of lethal skeletal dysplasia.
- It occurs approximately once in 20,000 births.
- The affected infants die within minutes or days of respiratory failure.
- This lethal disorder is associated with mutations in the fibroblast growth factor receptor 3.

# LIMB GIRDLES

- The development of the limb girdles remains incompletely investigated, but experimental work on the chick has shown that the blade of the scapula is derived from cells of the dermomyotome, whereas the remainder of the scapula arises from lateral plate mesoderm.
- The three bones of the pelvis all arise from lateral plate mesoderm, with no known contribution from the somites.
- Each of the bones of the pelvis, as well as the two developmentally different components of the scapula, is characterized by a different molecular signature.
- How the bones of the appendages are patterned to connect with their respective girdles is still poorly understood, but studies of mutants suggest that the transcription factors **Pbx-1** and **Pbx-2** play an important upstream role.

# THANK YOU