Development of the Axial Skeleton and Limbs

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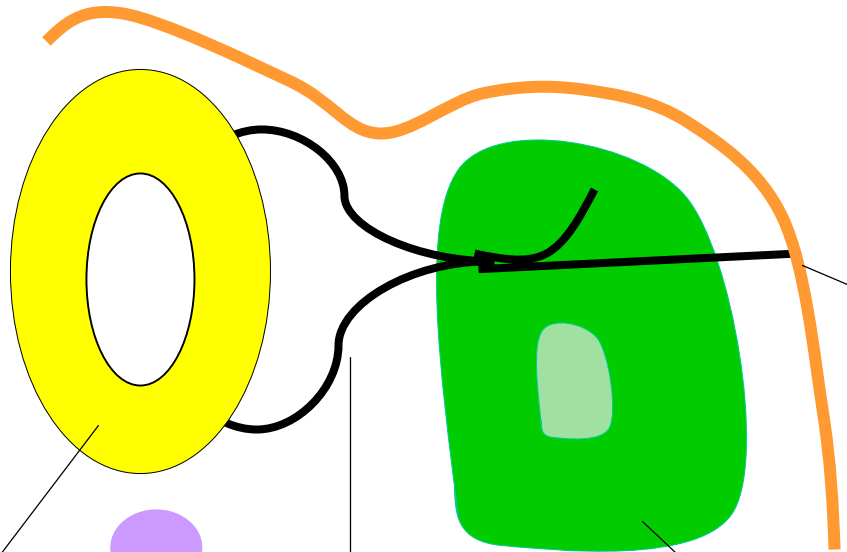
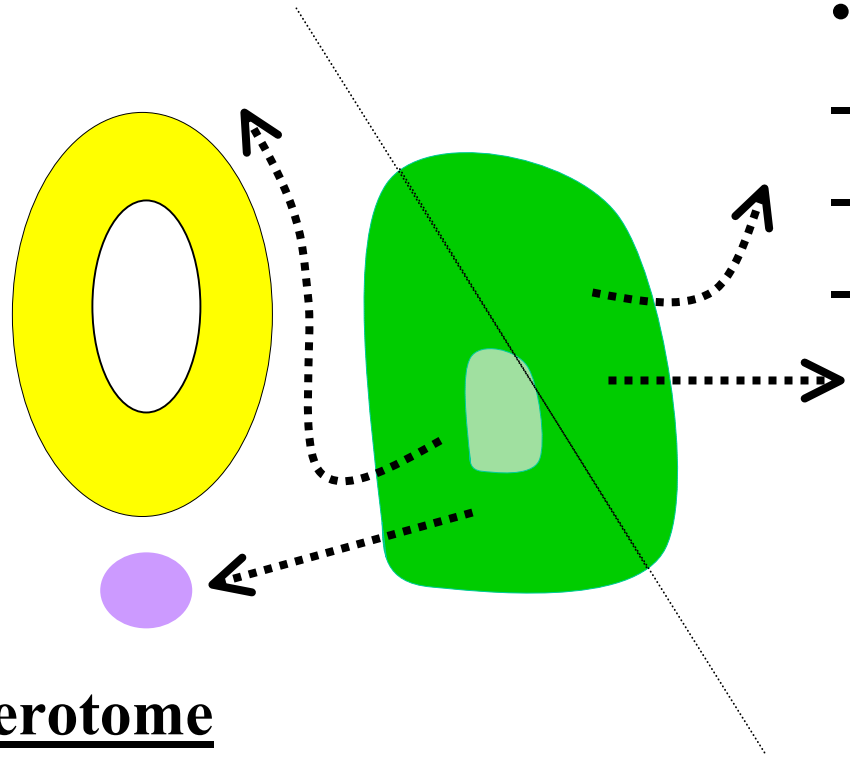
During the Fourth Week the Embryo Is Segmented.

Each segment consists of:



- a segment of neural tube
- a segmental nerve
- a somite
- overlying ectoderm

A Somite Is Divided Into Two Parts



- **Dermomyotome**
- **migrates laterally for form**
- **dermatome (dermis of skin)**
- **myotomes (skeletal muscle)**

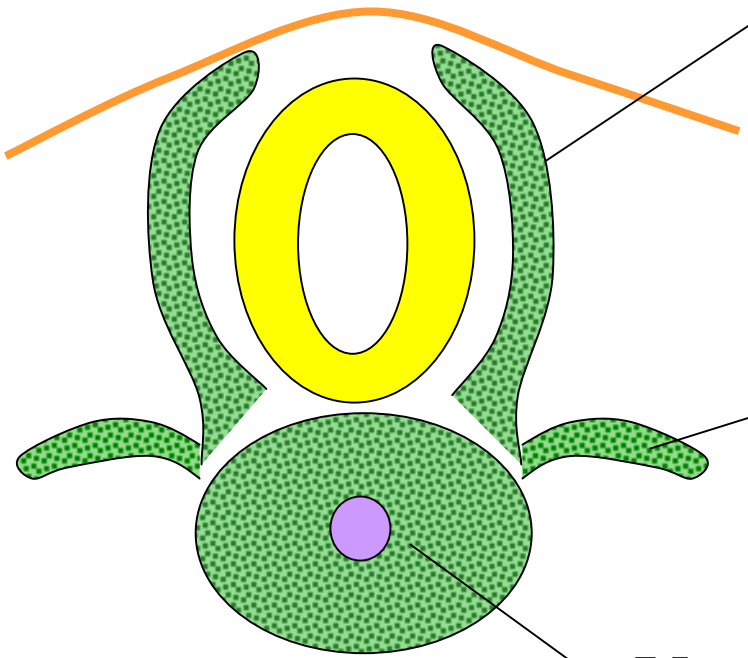
- **Sclerotome**

- contains a “cavity” of loose cells;

- migrates medially to surround the notochord and neural tube;

- forms the axial skeleton

Sclerotome Cells Migrate in Different Directions

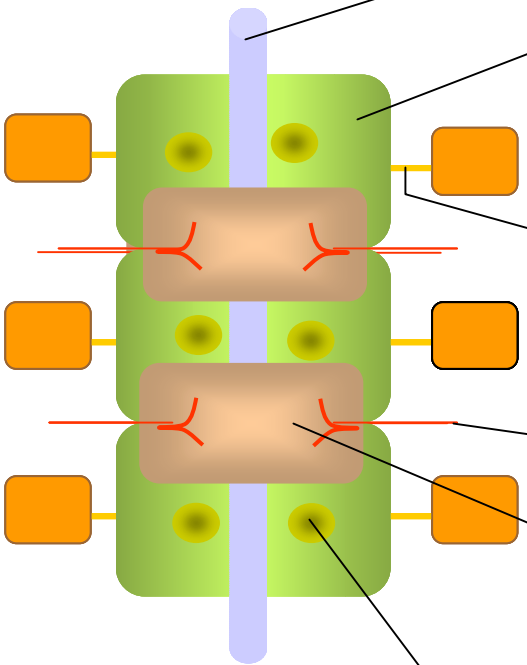


- Dorsomedially -
surround the neural tube and
form the neural arches

- Laterally -
form the costal elements

- Ventromedially -
surround the notochord and
form the vertebral bodies

The Vertebral Column Is Derived From Sclerotomes



- Sclerotomes surround the non- segmented notochord
- Each sclerotome is denser at the periphery than at the centre
- Segmental nerves entering the somites correspond to the sclerotomes
- Blood vessels are inter-segmental
- Vertebral centres develop around the blood vessels and form the vertebral bodies
- Primordia of intervertebral discs appear segmentally

Each Vertebral Body Is Derived From Two Adjacent Somites

- Each vertebra is formed from the caudal part of one sclerotome and the cranial part of the sclerotome below
- The vertebral number corresponds to the more caudal somite (and spinal nerve)
  - a spinal nerve emerges below the numerically corresponding vertebra
- Intervertebral discs correspond to the somite levels

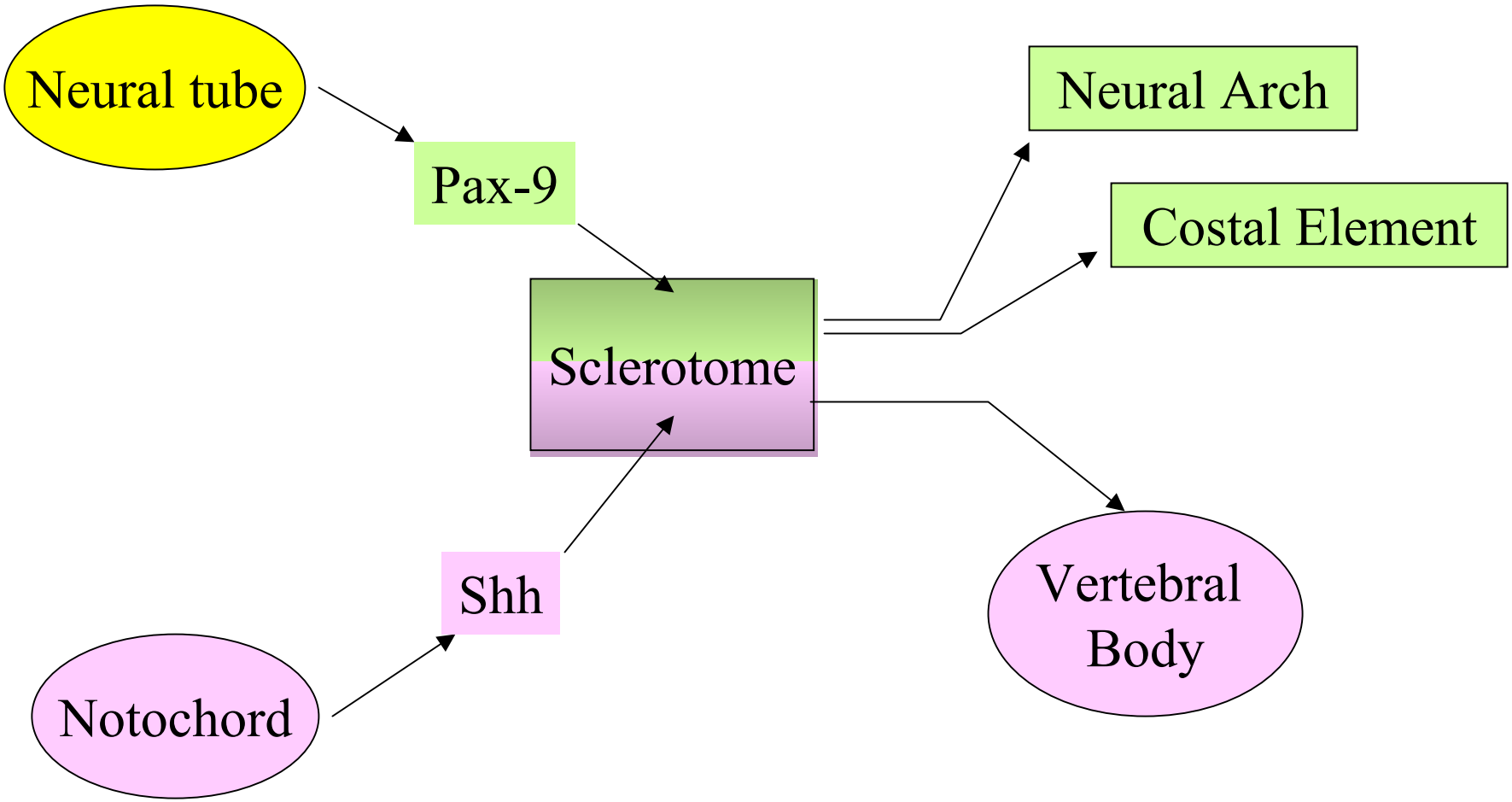
The Neural Arches and Costal Elements Are Inter-segmental

- The neural arches and costal elements both migrate from the sclerotomes.
- The segmental spinal nerves all lie below the neural arches and the ribs
- The intervertebral foramina are formed by contributions from the vertebra above and the vertebra below

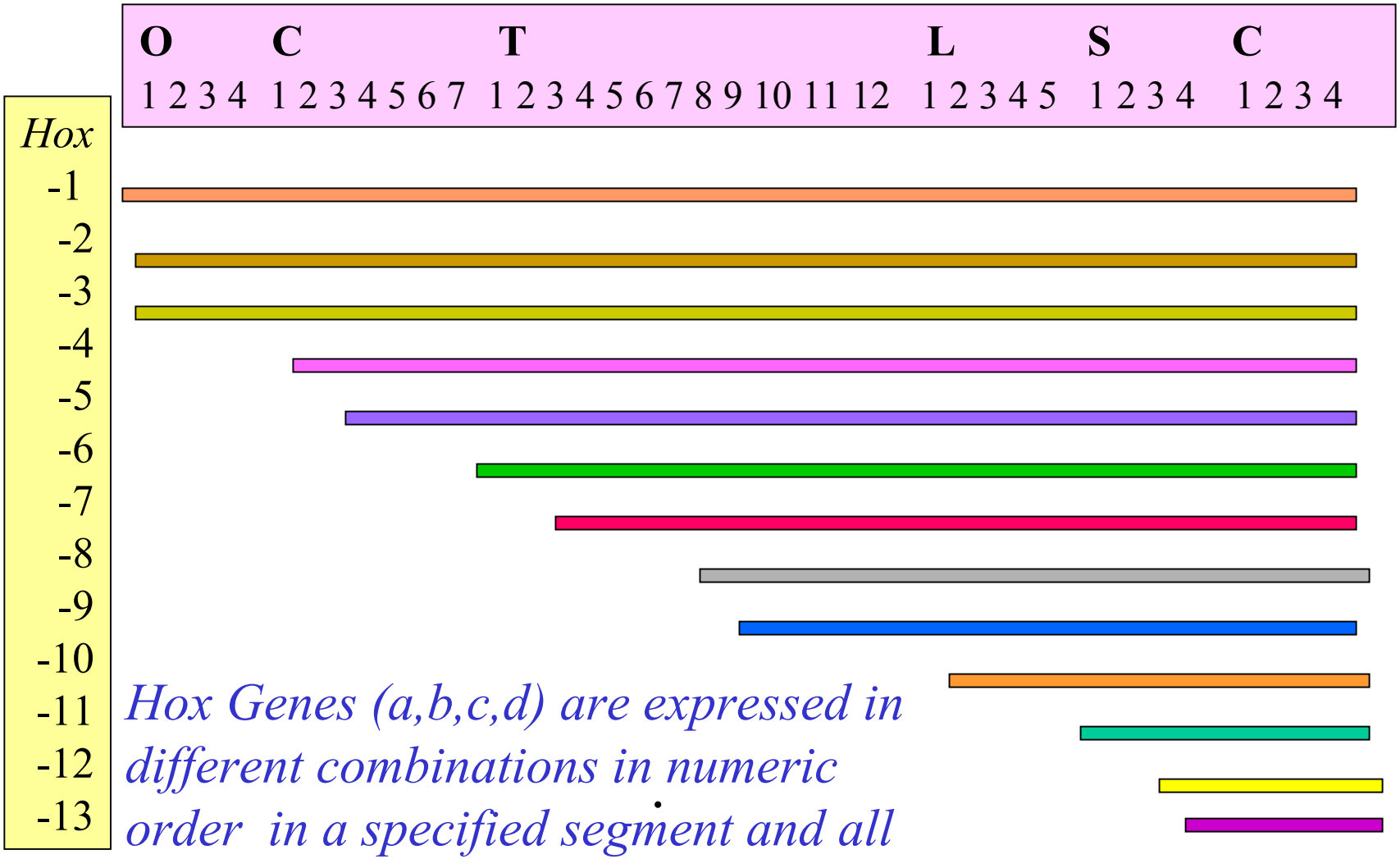
The Cervical Spinal Nerves Are Wrongly Numbered

- Occipital – incorporated into the skull
- C1 is the suboccipital nerve
- Cervical – 7
- Thoracic –12
- Lumbar –5
- Coccygeal – 4 (rudimentary in humans)

The Vertebral Bodies and Neural Arches Are Separately Determined

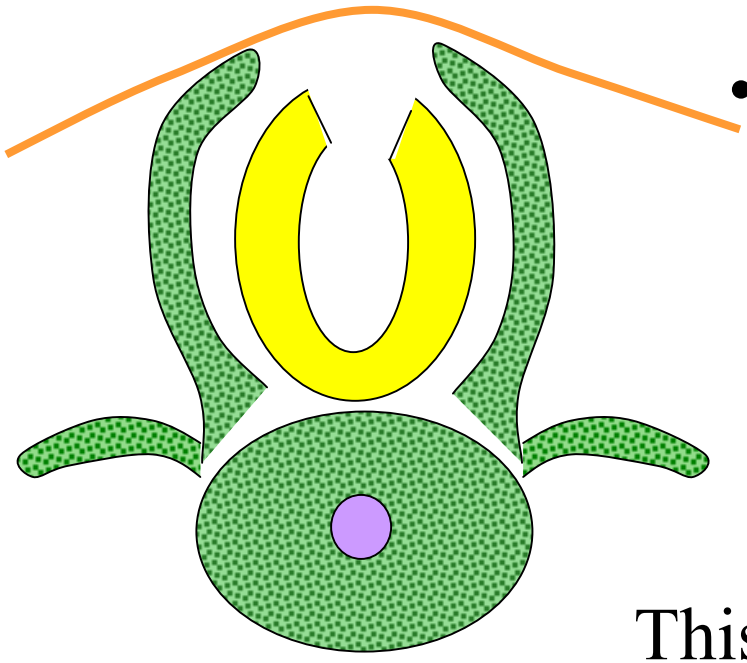


Expression of Hox Genes Along Vertebral Axis



Hox Genes (a,b,c,d) are expressed in different combinations in numeric order in a specified segment and all the more caudal ones.

The Neural Tube Induces the Formation of the Neural Arches.

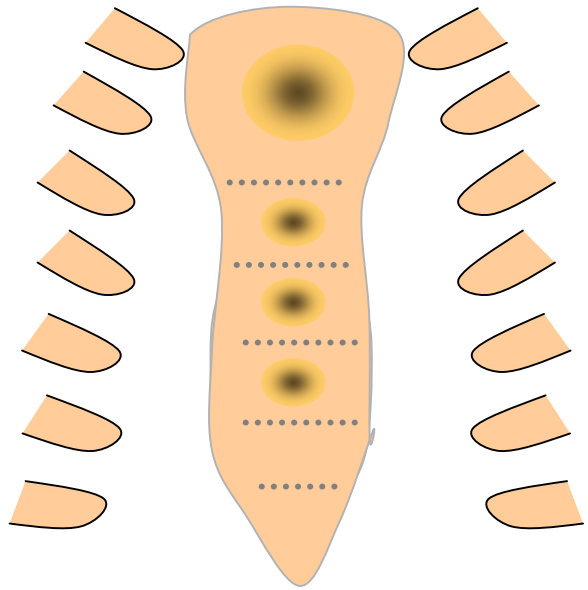


- Defects in the closure of the neural tube will also cause failure of development of the overlying neural arches and their fusion across the midline.

This occurs in meningomyelocoele

A Pair of Sternal Bars Form in the Ventral Body Wall

- The first seven rib elements converge and fuse with the sternal bars in the 7th week

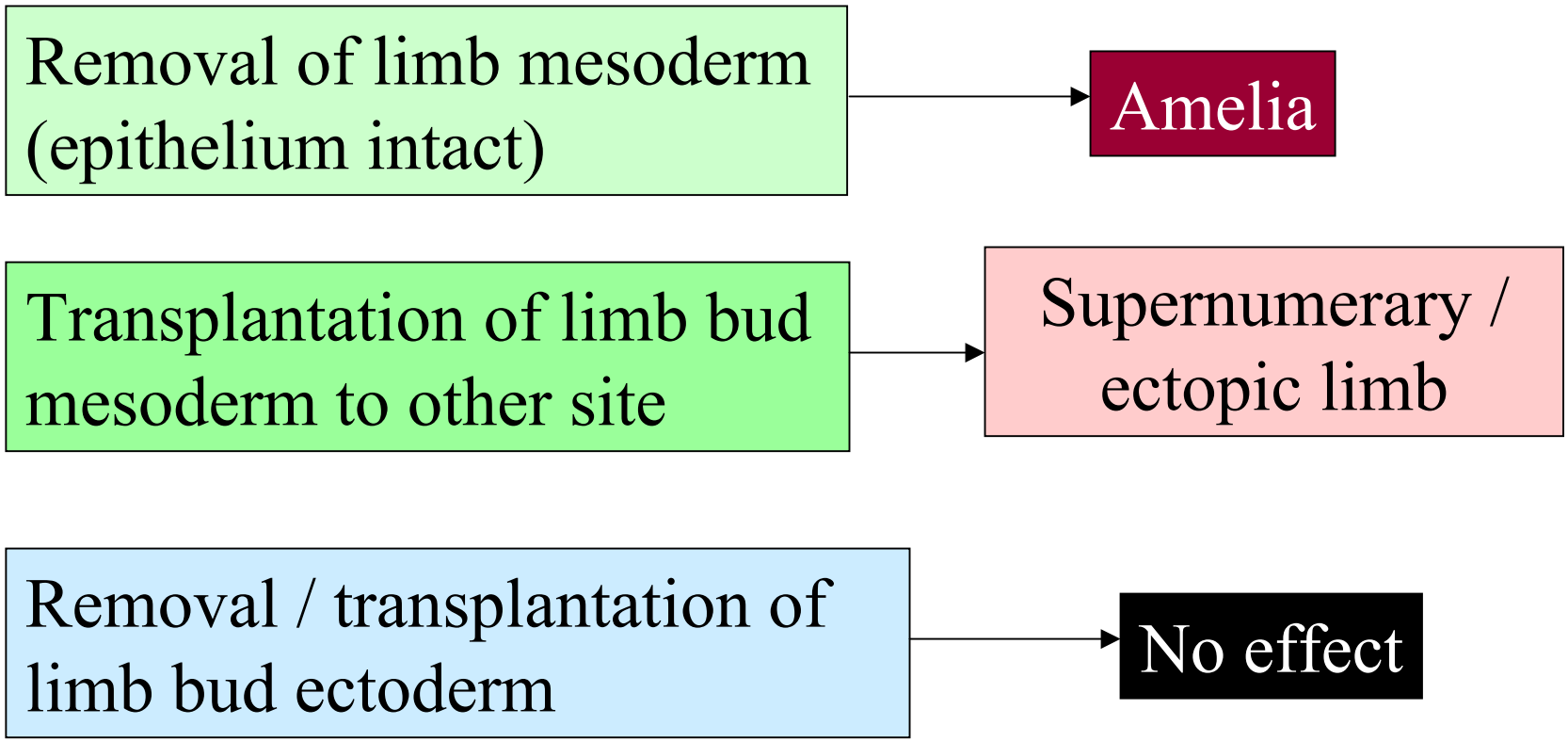


- The sternal bars fuse across the midline commencing in the most cranial part and extending caudally
- Ossification in the cartilaginous sternum occurs in 5 pairs of primary centres, forming five sternebrae.

The Limb Primordia

- Develop in the somatopleure of the lateral plate mesoderm
- Upper limb primordium
  - On day 24 in lower cervical region
- Lower limb primordium
  - On day 28 in lower lumbar region

Early Limb Development Is Dependent on the Limb Bud Mesoderm



Morphogenesis of Limbs

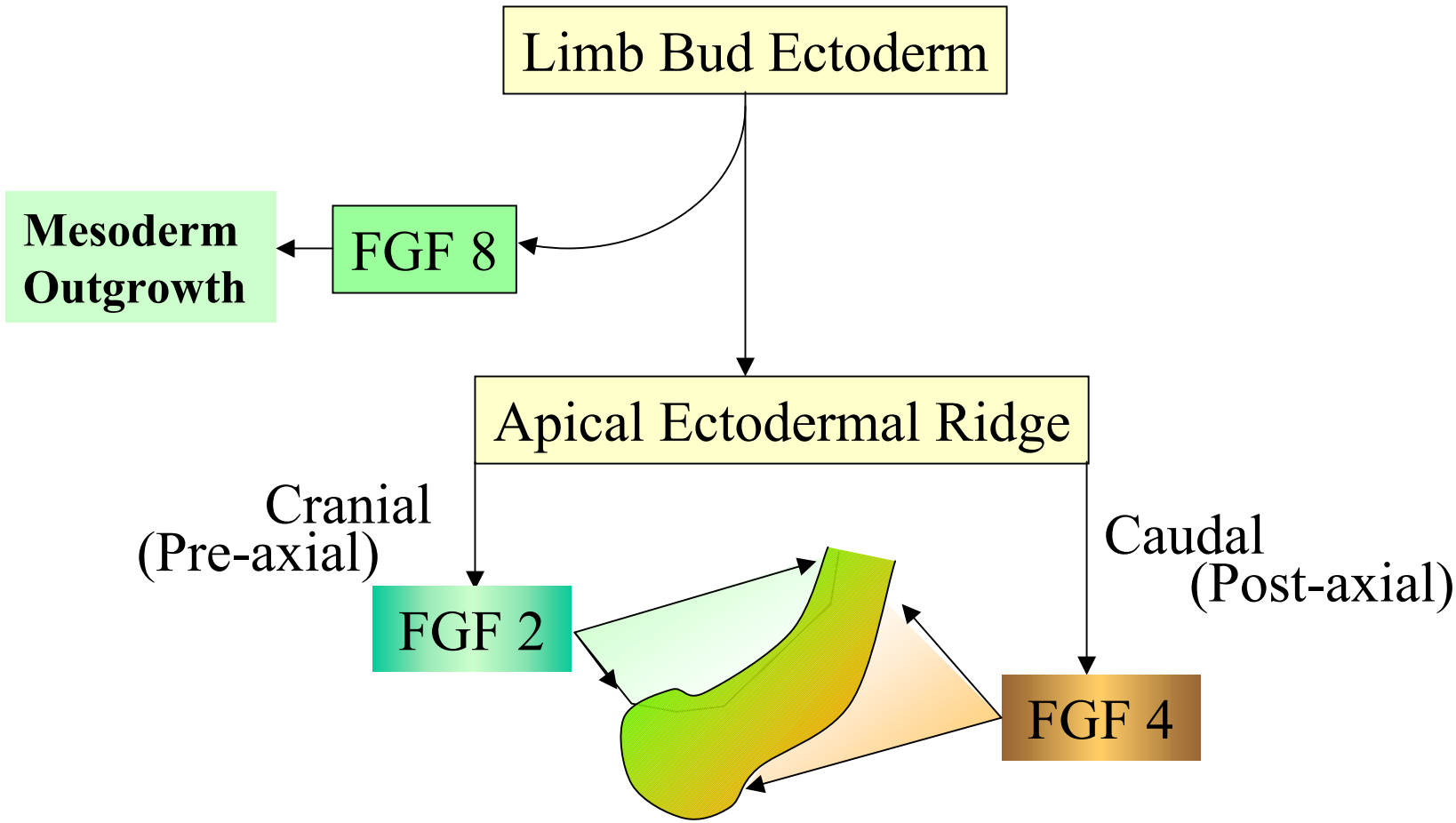
Three centres in the limb bud primordium determine three limb axis:

- Apical ectodermal ridge
  - Determines proximo-distal segments
- Zone of polarising activity (ZPA)
  - Determines cranio-caudal axis
- Dorsal and ventral ectoderm
  - Determine dorso-ventral axis

The Apical Ectodermal Ridge

- Is an ectodermal thickening
- Runs along the distal margin of the limb bud (craniocaudally)
- Is essential for limb bud development
  - *Removal of AER leads to failure of limb growth & development (phocomelia)*
- Determines time-dependent differentiation of the proximal-distal limb bud mesoderm:
  - *Early mesoderm forms proximal limb segment*
  - *Late mesoderm forms distal limb segment*
- Expresses FGF-8, FGF-2, FGF-4

Molecular Determination of Limb Bud Development

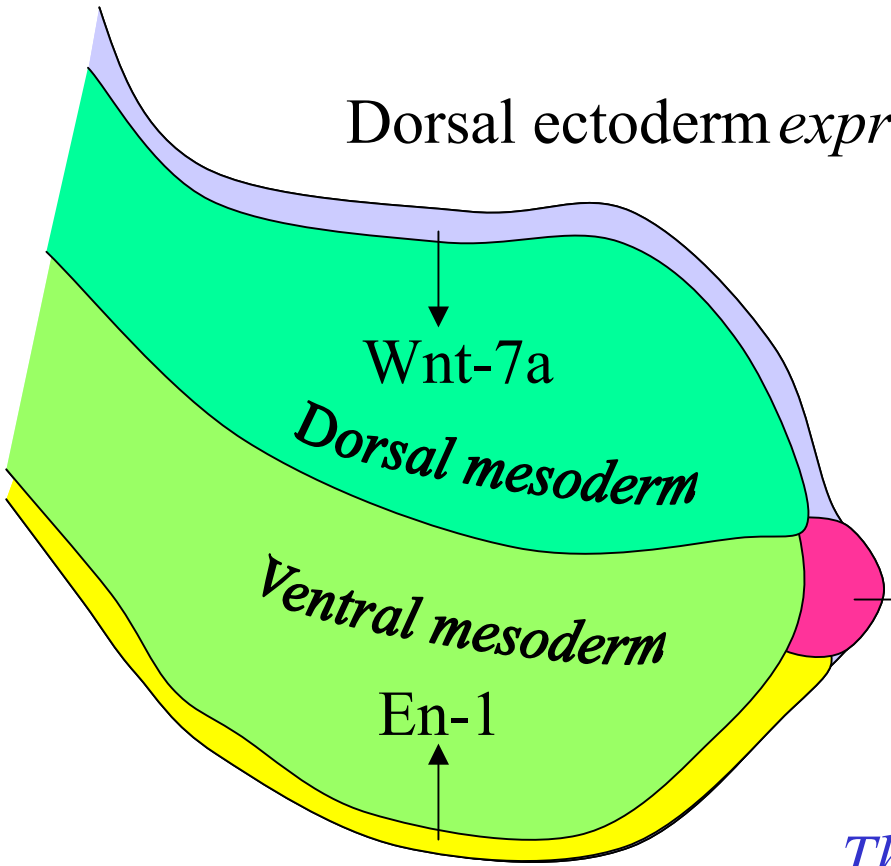


The Zone of Polarizing Activity (ZPA)

- Is a region of mesoderm in the dorsal part of the limb bud
- Determines the cranio-caudal axis

  (pre-axial and post-axial margins)
- Maintains the apical ectodermal ridge
- Expresses sonic hedgehog
- ZPA transplant stimulates the formation of a second AER, and growth of a supernumerary limb.
- A retinoic acid implant produces a similar effect to a transplanted ZPA.

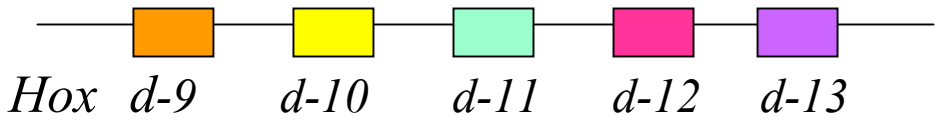
Dorso-ventral Mesoderm Patterning Is Determined by Ectoderm

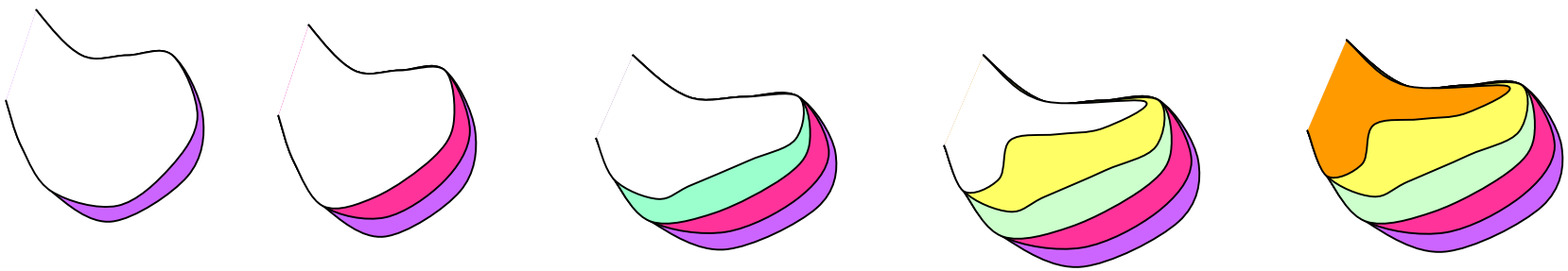


The Wnt family is associated with cell-surface and extracellular matrix

Hox Genes Are Regionally Expressed in the Limb Buds

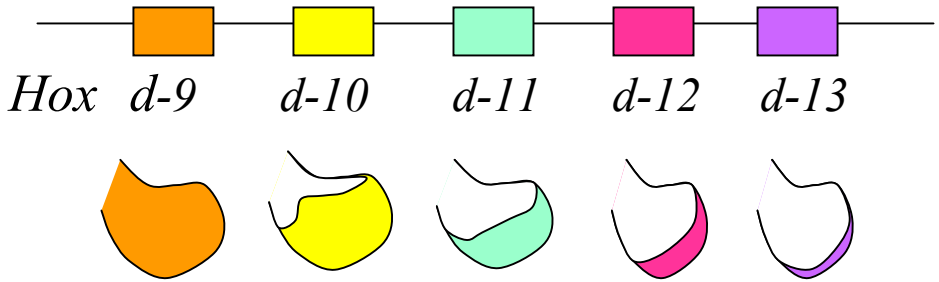
The Hox genes expressed in the limb buds are:
Clusters *Hoxd* and *Hoxa* - genes 9 to 13 in each cluster
Expressed in distal to proximal (13 to 9) sequence

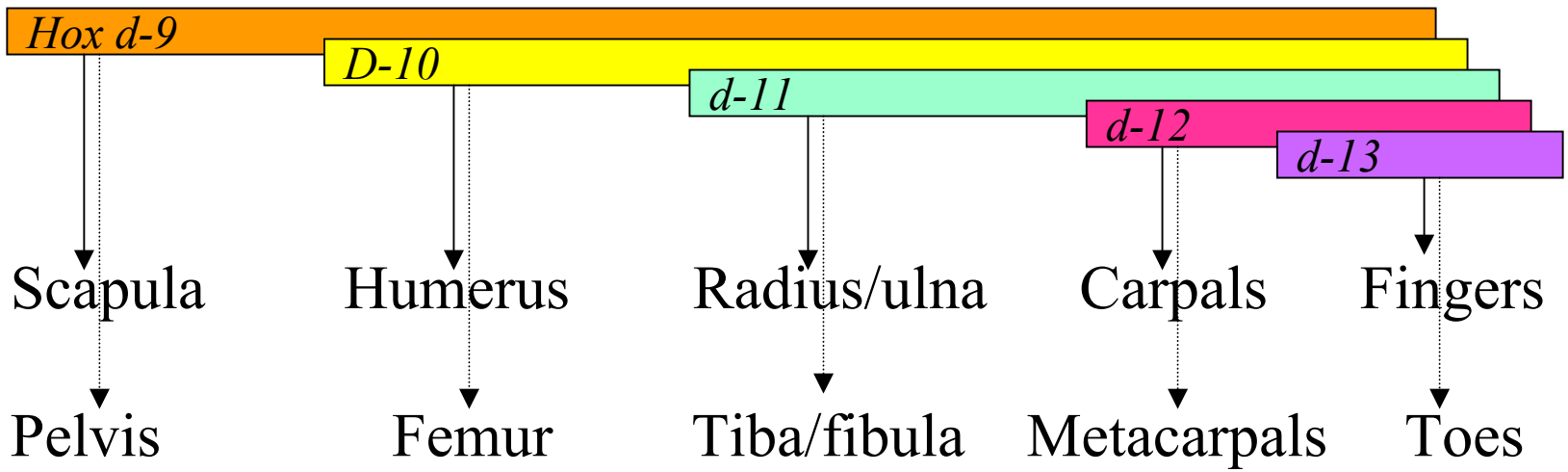




Overlapping Hoxd Genes Are Expressed in Definitive Limb Segments

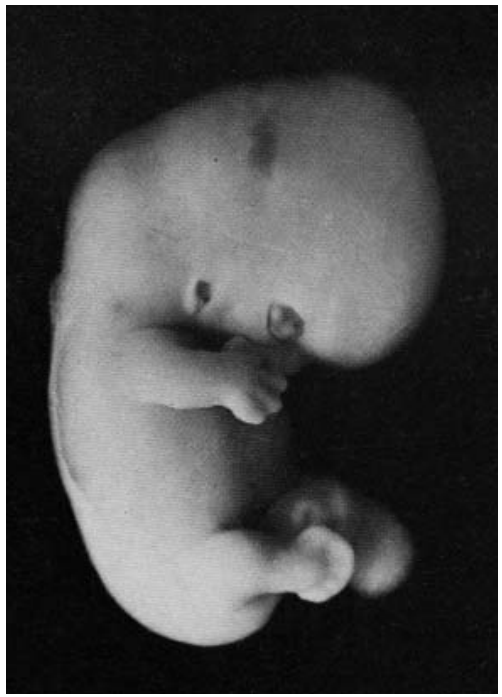
Overlapping expressions in distal to proximal segments



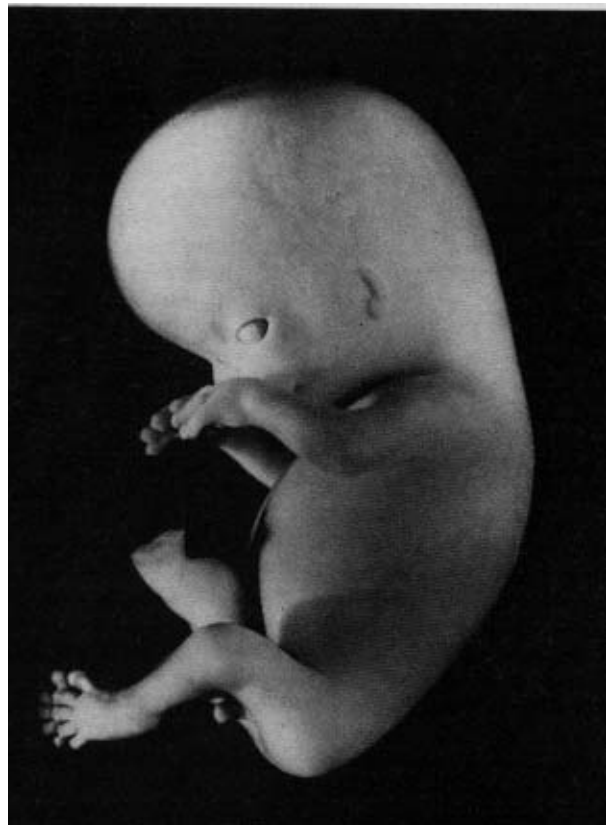


Stages in Development of Limbs

6 weeks

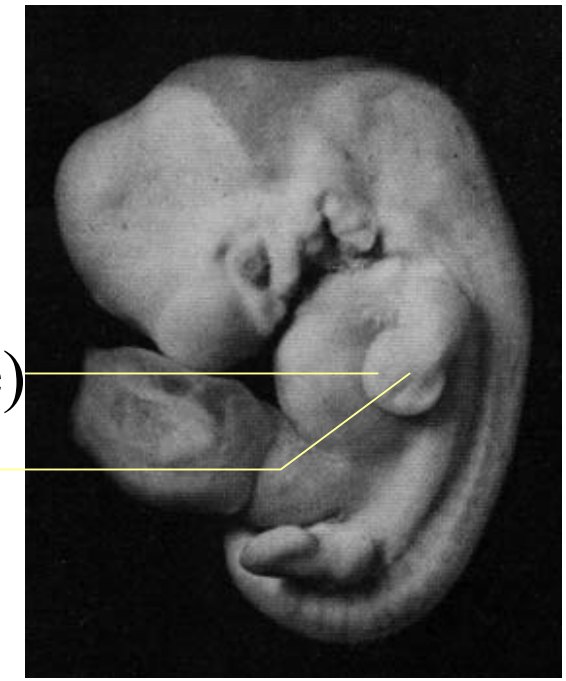


7 weeks



8 weeks

Stages in Development of Upper Limb



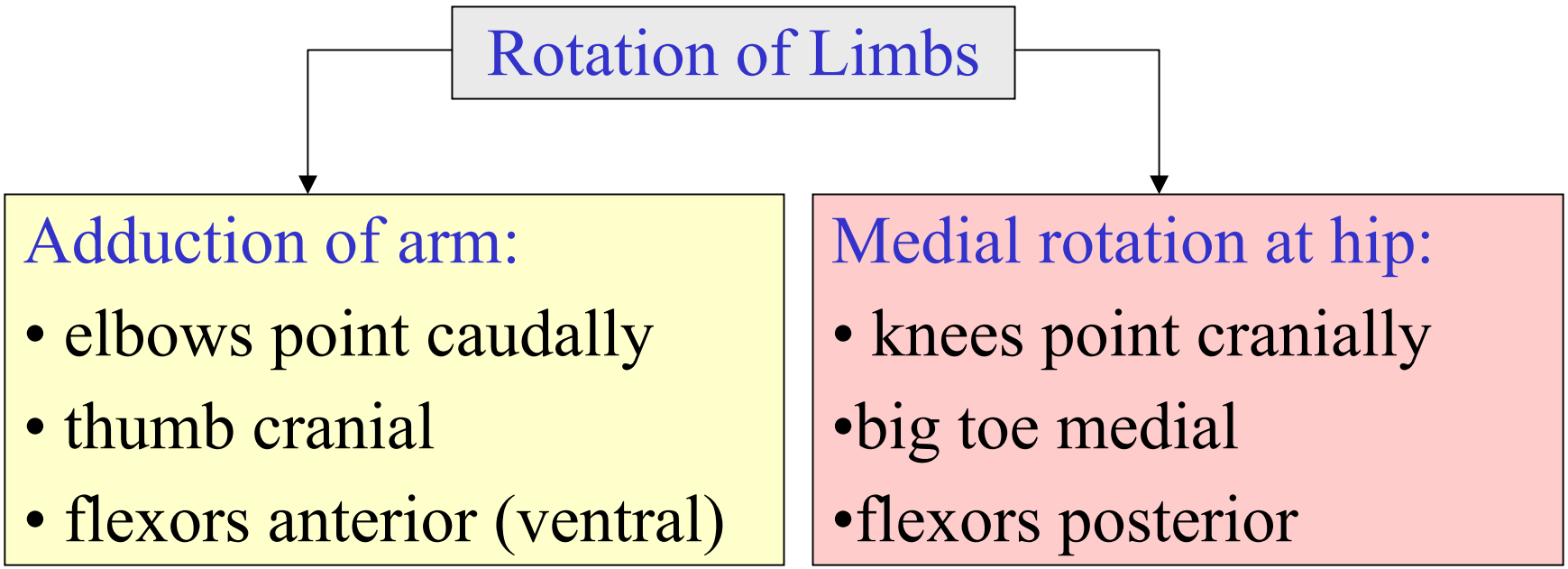
- 29 days: appearance of limb buds
- 33 days: hand plate
  forearm, arm & shoulder
- 37 days: digital plate (thick distal ridge)
  carpal region (central)
  forearm and arm distinct
- 38 days: finger rays
  (indentations outline finger tips)
- 42 days: deep notches separate fingers
- 52 days: fetal pads (distal swellings) on fingers

Stages in Development of Lower Limb

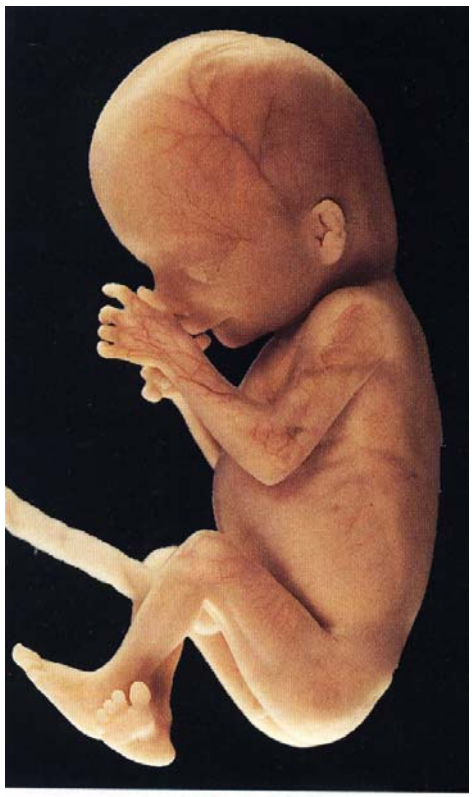
- Lags behind upper limb by 3 to 7 days
- 32 days: appearance of lower limb buds
- 37 days: thigh, leg and foot plate
- 44 days: tarsal region and toe rays
- 52 days: indentations outline toes
- 56 days: toes fully formed

Flexion and Rotation of Limbs Occur Between 6th and 8th Weeks

- Pre-axial borders marked by thumb / big toe
- Flexion occurs at elbow and knee

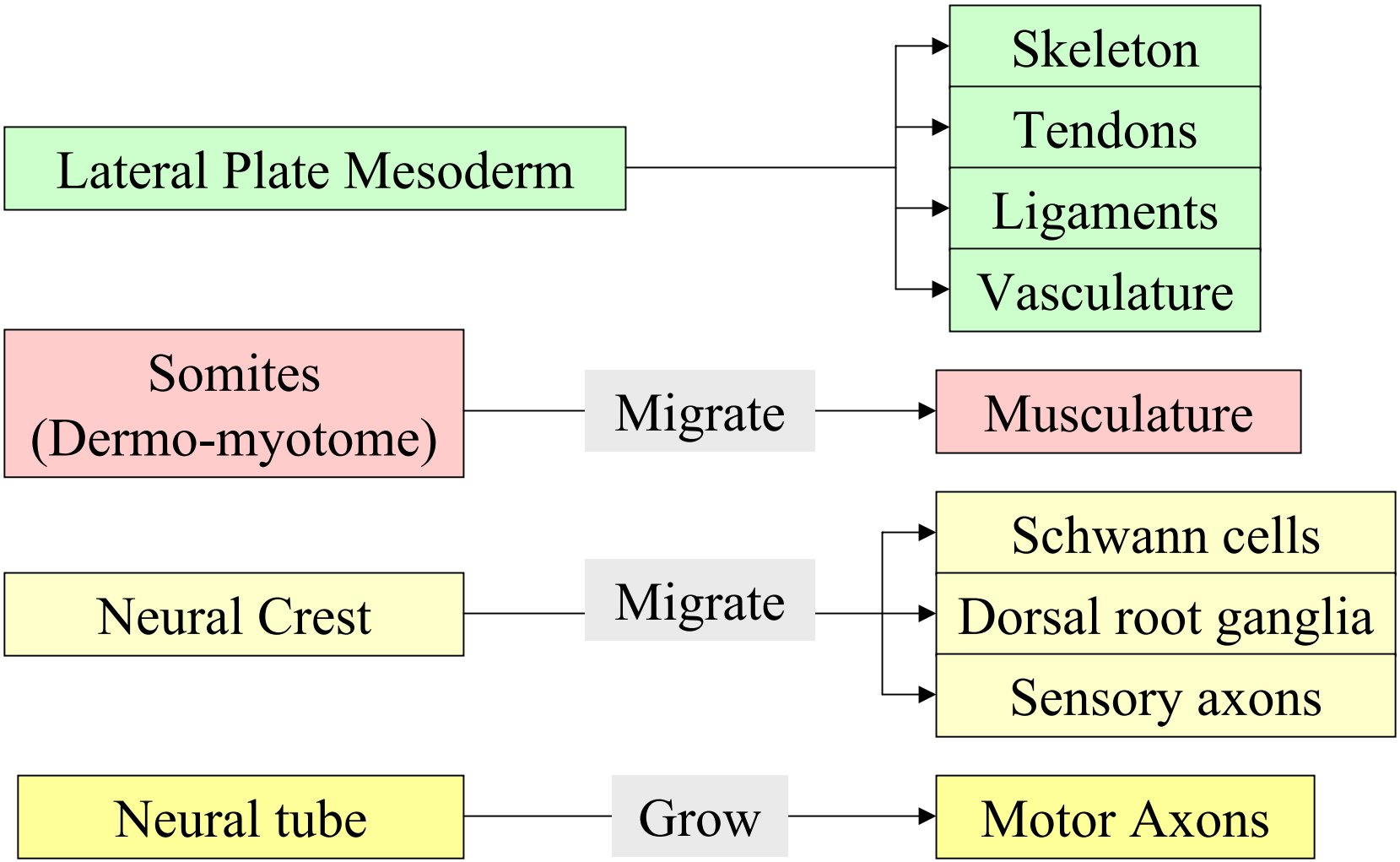


Does the Upper Limb Undergo Adduction or Lateral Rotation?

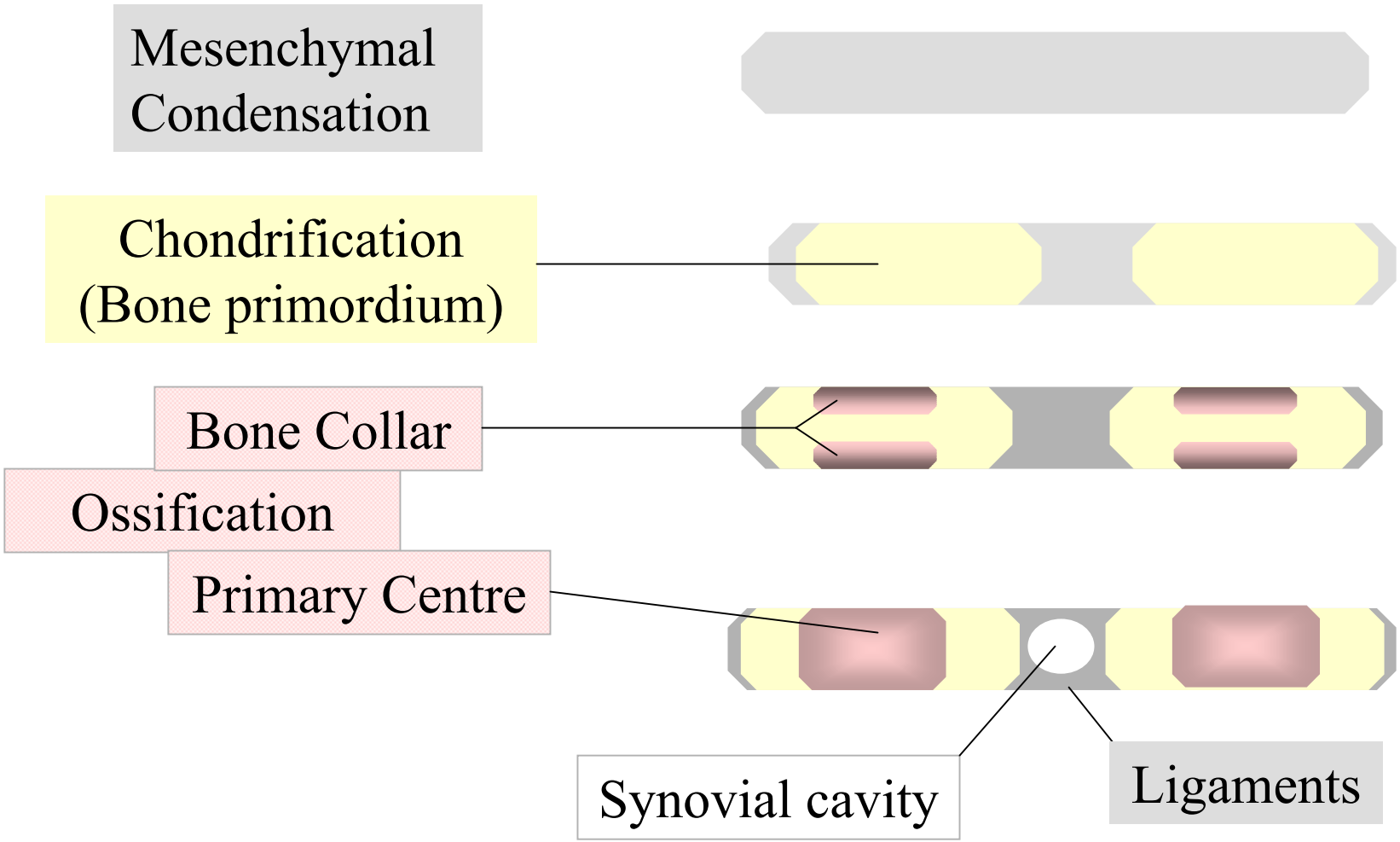


- Simple adduction at the shoulder and flexion at elbow brings upper limb to natural foetal position (thumb cranial; palm facing medially)
- Lateral rotation brings upper limb to anatomical position (palm facing anteriorly, thumb lateral)

Development of Limb Tissues Is From Four Sources



The Limb Bones Form by Endochondral Ossification



Congenital Anomalies of Limbs

- Reduction defects:
  - Amelia – absent whole limb
  - Meromelia – absent or rudimentary part of a limb
  - Phocomelia – rudimentary, poorly differentiated limb
  - Hemimelia – rudimentary distal limb segment
  - Adactyly – absence of all fingers
  - Ectrodactyly – missing fingers

  (Many are defects of AER determining proximal-distal patterning)
  - Radial / tibial reduction defect – absence of radius or tibia +/- absent or abnormal thumb/big toe

Congenital Anomalies of Limbs

- Duplication defect
  - Polydactyly – pre-axial or post-axial

  (defect in cranio-caudal patterning – ZPA defect)
- Differentiation defect
  - Syndactyly

  (Some are defect of *Hoxd-13*)
  - Sirenomelia – "fused" lower limb
  - (defect of caudal mesoderm)
  - Talipes (clubfoot) – abnormal structure/position of foot

Causes of Limb Defects may be:

- Genetic
- Teratogenic
- Mechanical

Causes of Limb Defects

1. Genetic

- some cases of polydactyly, syndactyly, brachydactyly, lobster claw hand are autosomal dominant disorders
- Many limb defects are components of genetic syndromes

Causes of Limb Defects

2. *Teratogenic*

- Drugs and chemicals
  - Thalidomide (inadequately tested drug)
  - Dimethadione (an anti-epileptic drug)
  - Retinoic acid (used for treatment of acne)
  - Cadmium (an environmental teratogen)

  (Many chemicals have been used experimentally to study limb teratogenicity.)
- Viruses
- Radiation
- Hypothermia and hyperthermia

Causes of Limb Defects

3. Mechanical

- Amniotic bands may cause disruption or amputation of part of a limb
- Foetal compression e.g. oligohydramnios is a cause of talipes;
- Uterine defect e.g. bicornuate uterus