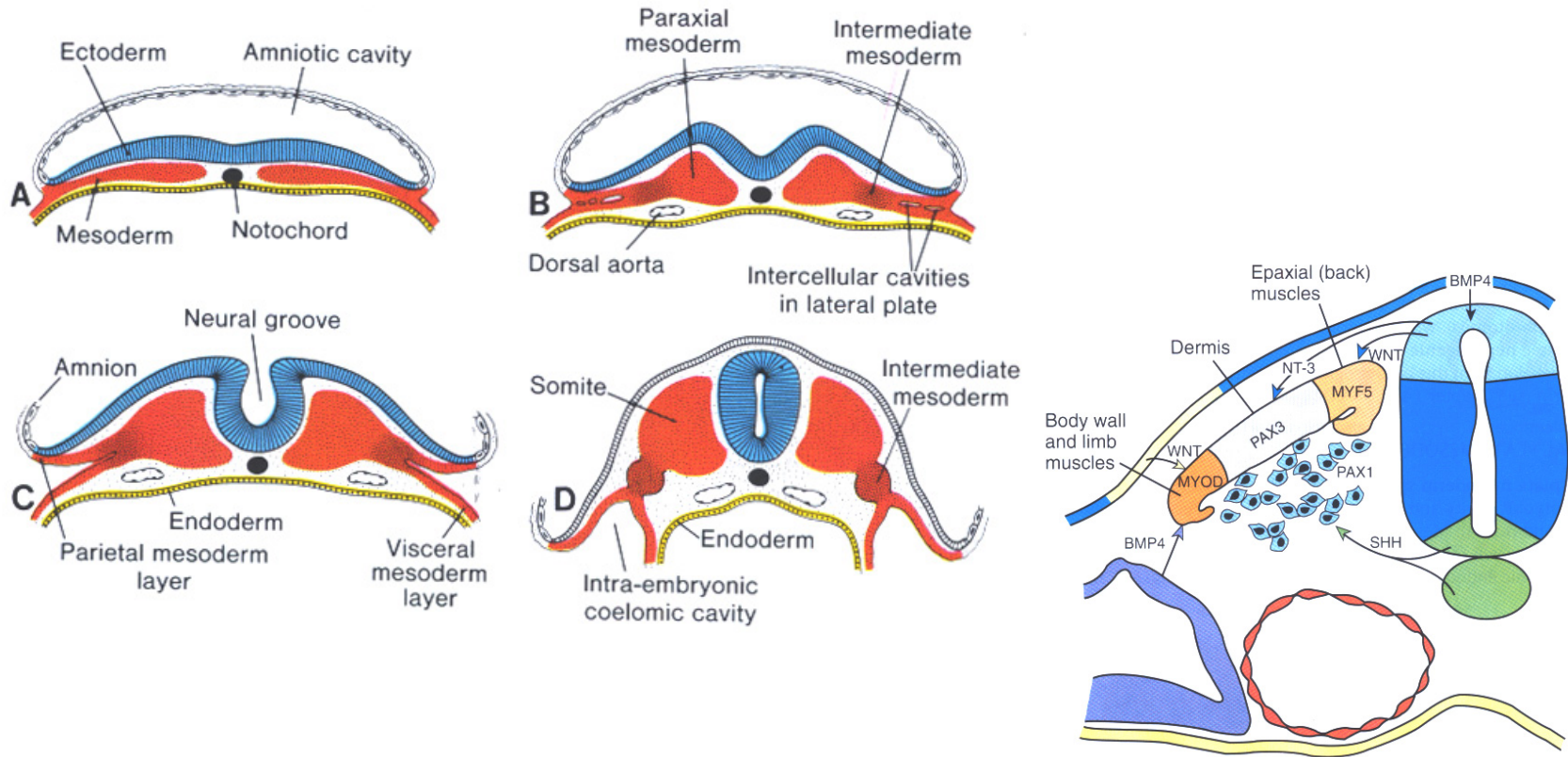


Development of the Musculoskeletal System

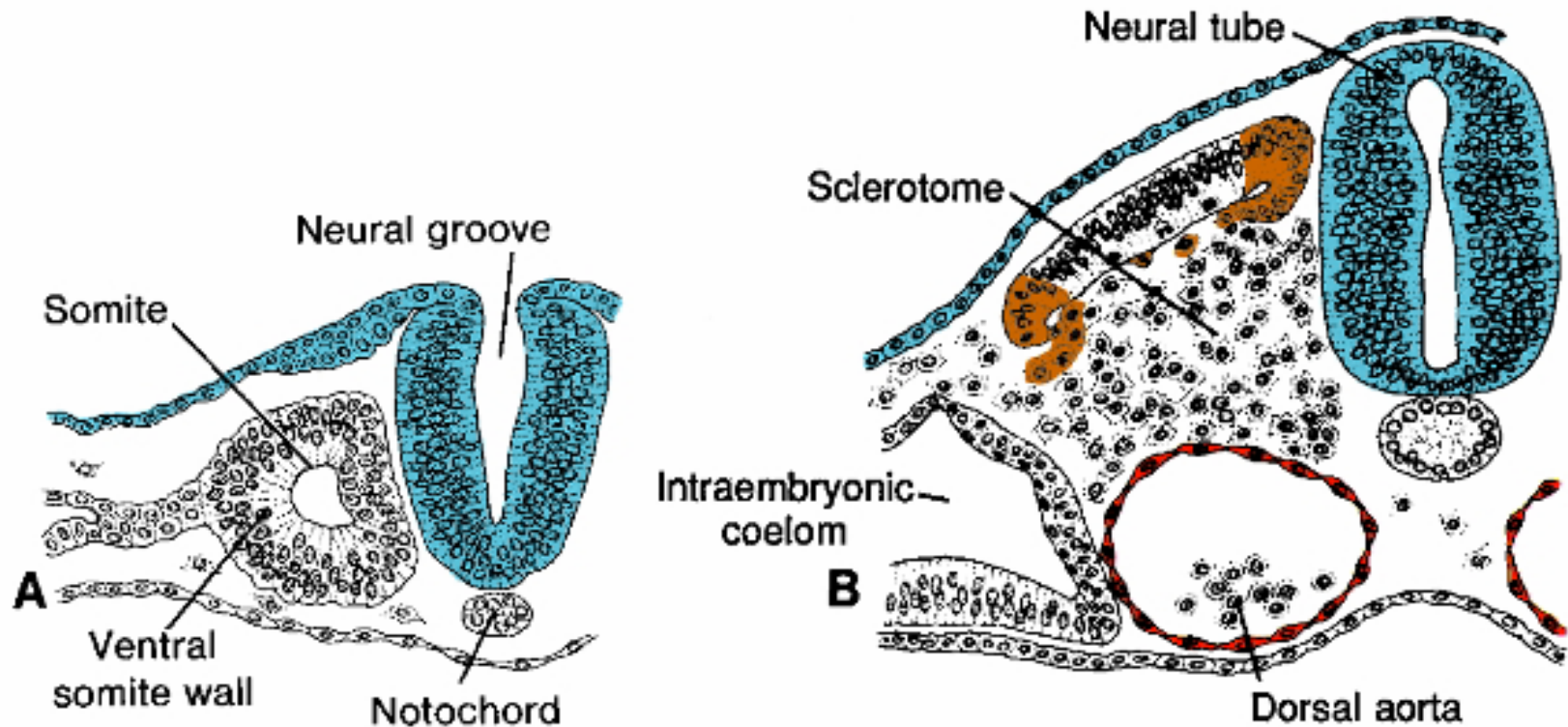
Week 14

Skeletal System



Derived from:

- paraxial mesoderm → somites and somitomeres → sclerotome
 - sclerotome differentiation induced by SHH from notochord and floor plate
- somatic lateral plate mesoderm → contributes to pelvis, shoulders and limbs
- neural crest → contributes to face and skull



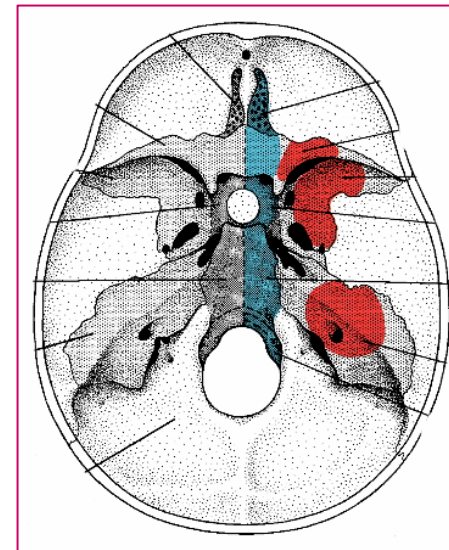
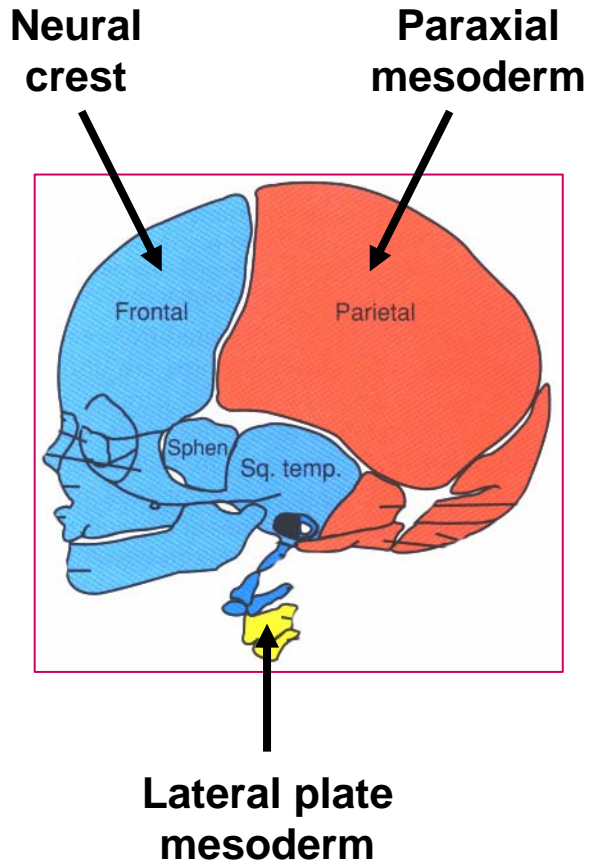
Ventral wall of somite → sclerotome

Sclerotome → mesenchyme (loose connective tissue)

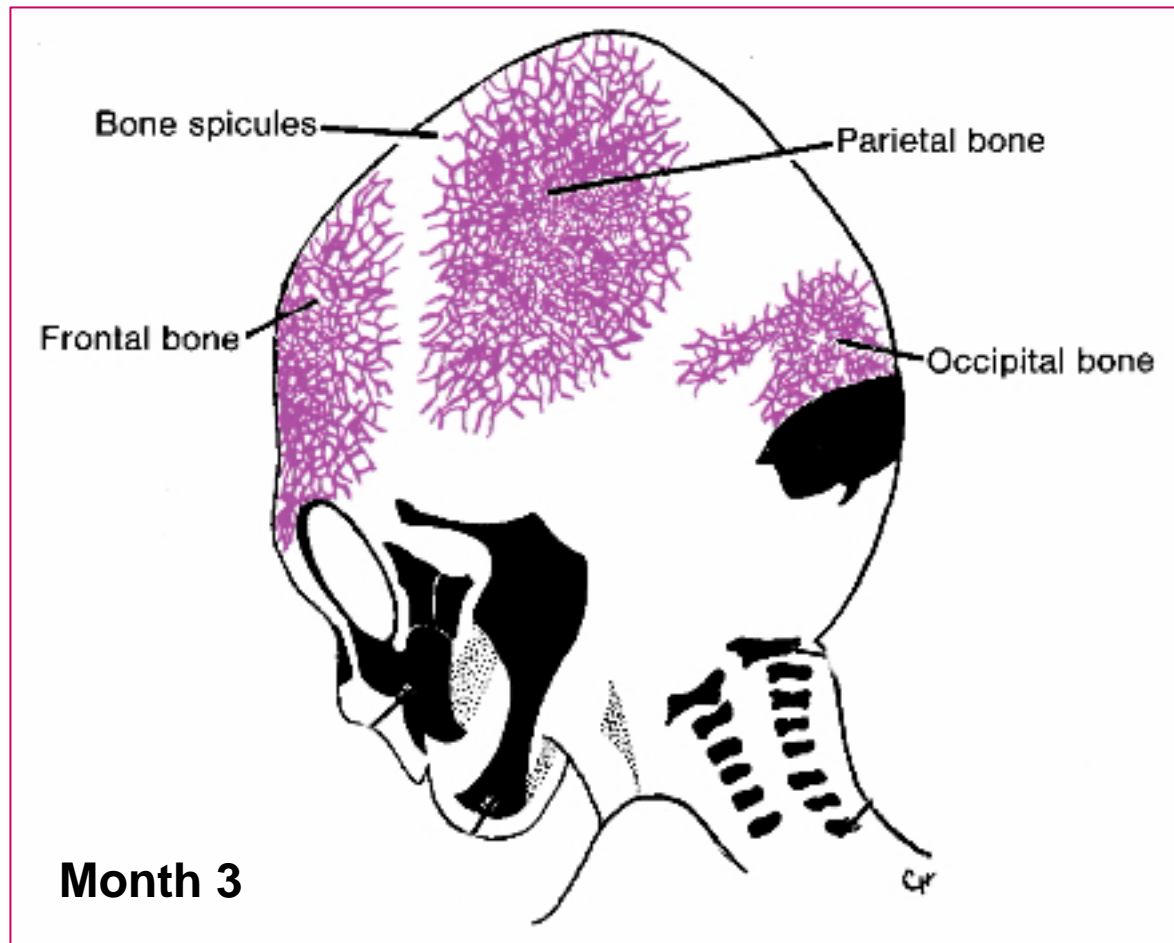
Mesenchyme → osteoblasts (bone) and chondroblasts (cartilage)

Skull

- **Neurocranium**
 - membranous neurocranium = vault of skull
 - forms by intramembranous ossification
 - chondrocranium = base of skull
 - forms by endochondrial ossification from cartilage model
- **Viscerocranium = face**
 - forms by endochondrial ossification

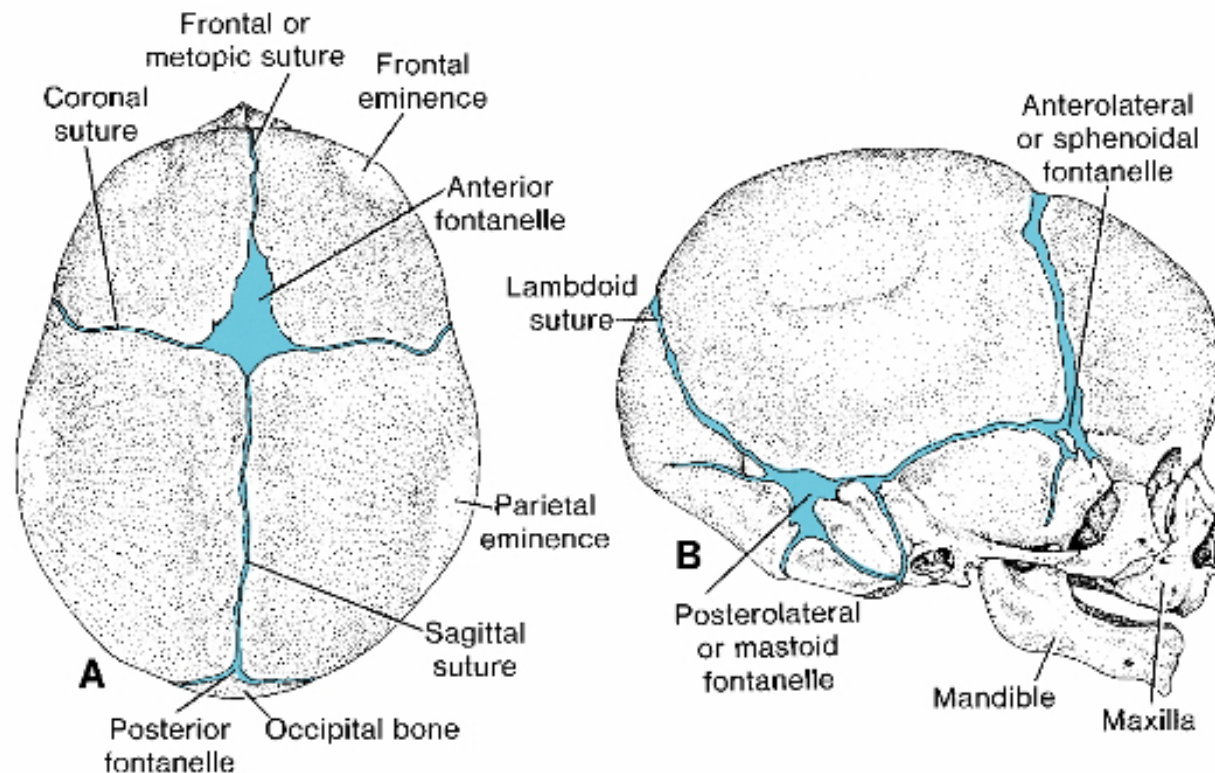


Flat bones of membranous neurocranium form by intramembranous ossification



Sutures

- Form between flat bones
- Fontanelles form where two sutures meet
- Connective tissue derived from neural crest and paraxial mesoderm
- May remain membranous until early adulthood





Anencephaly

- Failure to close anterior neuropore
- Associated with cranioschisis (failure to form cranial vault)
- Lethal

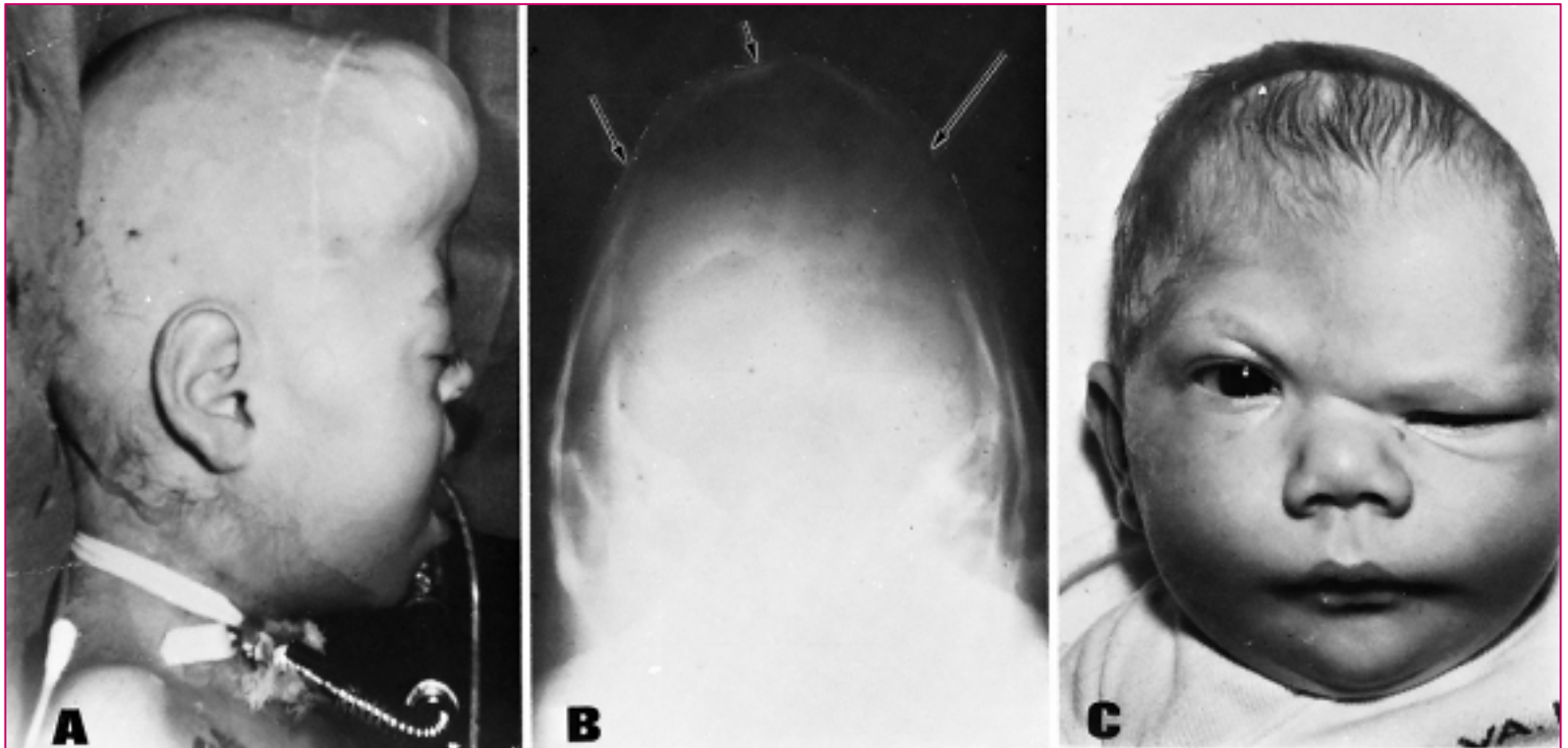


Meningocele

- Relatively small skull defect
- Outcome depends on extent of neural damage

Craniosynostosis

- Premature closure of sutures
- Involves dysregulation of FGF or TGF- β



Achondroplasia

- Defects in endochondrial ossification and growth of long bones and chondrocranium
- Involves mutations in FGF receptor-3

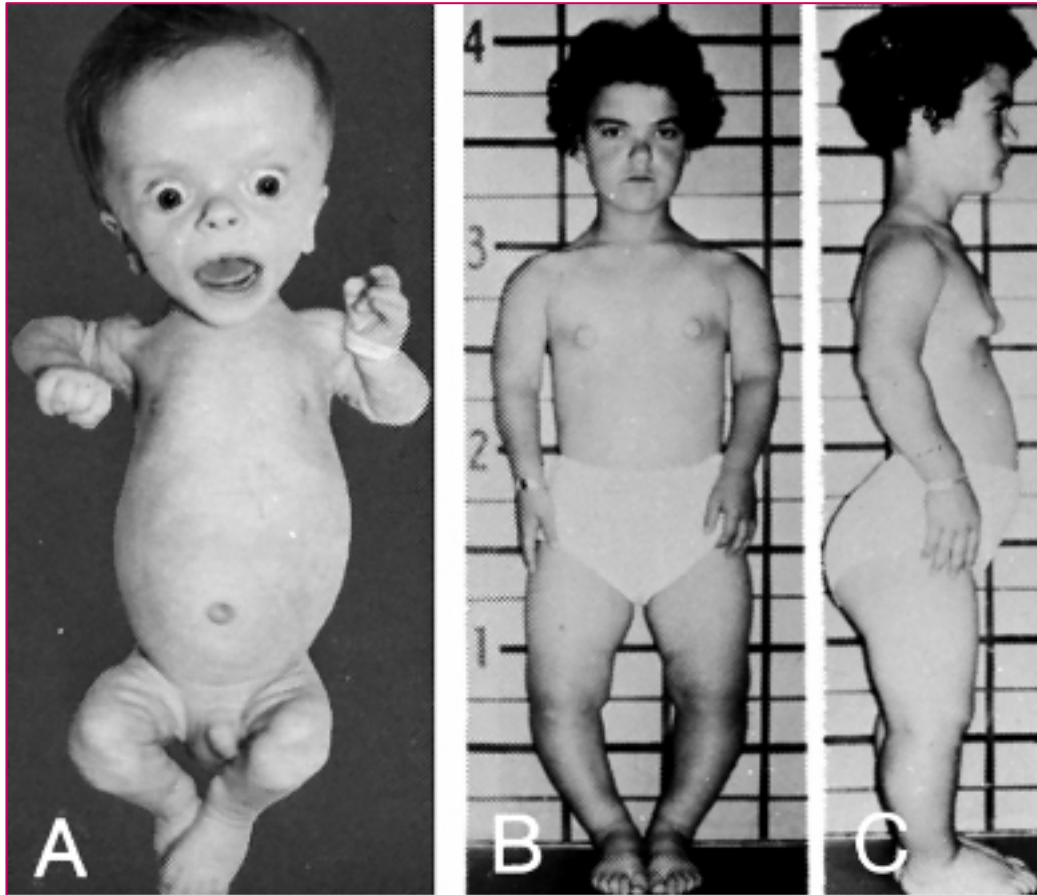


TABLE 8.1 Genes Associated With Skeletal Defects

Gene	Chromosome	Abnormality	Phenotype
FGFR1	8p12	Pfeiffer syndrome	Craniosynostosis, broad great toes and thumbs, cloverleaf skull, underdeveloped face
FGFR2	10q26	Pfeiffer syndrome	Same
		Apert syndrome	Craniosynostosis, underdeveloped face, symmetric syndactyly of hands and feet
		Jackson-Weiss syndrome	Craniosynostosis, underdeveloped face, foot anomalies, hands usually spared
FGFR3	4p16	Crouzon syndrome	Craniosynostosis, underdeveloped face, no foot or hand defects
		Achondroplasia	Short-limb dwarfism, underdeveloped face
		Thanatophoric dysplasia (type I)	Curved short femurs, with or without cloverleaf skull
		Thanatophoric dysplasia (type II)	Relatively long femurs, severe cloverleaf skull
		Hypochondroplasia	Milder form of achondroplasia with normal craniofacial features
MSX2	5q35	Boston-type craniosynostosis	Craniosynostosis
TWIST	7p21	Saethre-Chotzen syndrome	Craniosynostosis, midfacial hypoplasia, cleft palate, vertebral anomalies, hand and foot abnormalities
HOXA13		Hand-foot-genital syndrome	Small, short digits, divided uterus, hypospadias
HOXD13	2q31	Synpolydactyly	Fused, multiple digits

Week 4



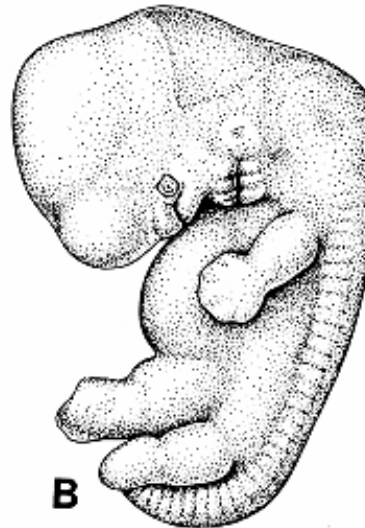
Development of Limb Buds

- **Begins in week 4**
- **Outgrowth of body wall mesenchyme (lateral plate mesoderm)**
- **Position on craniocaudal axis defined by Hox gene pattern**

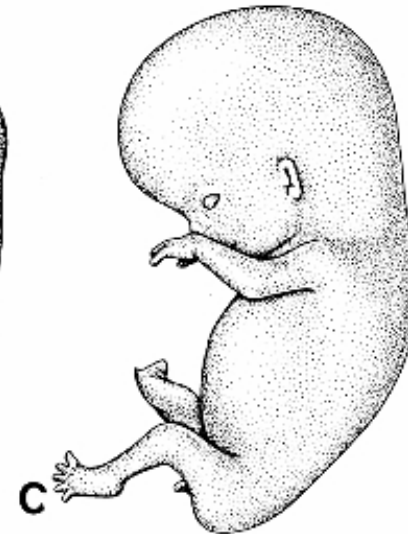
Week 5



Week 6

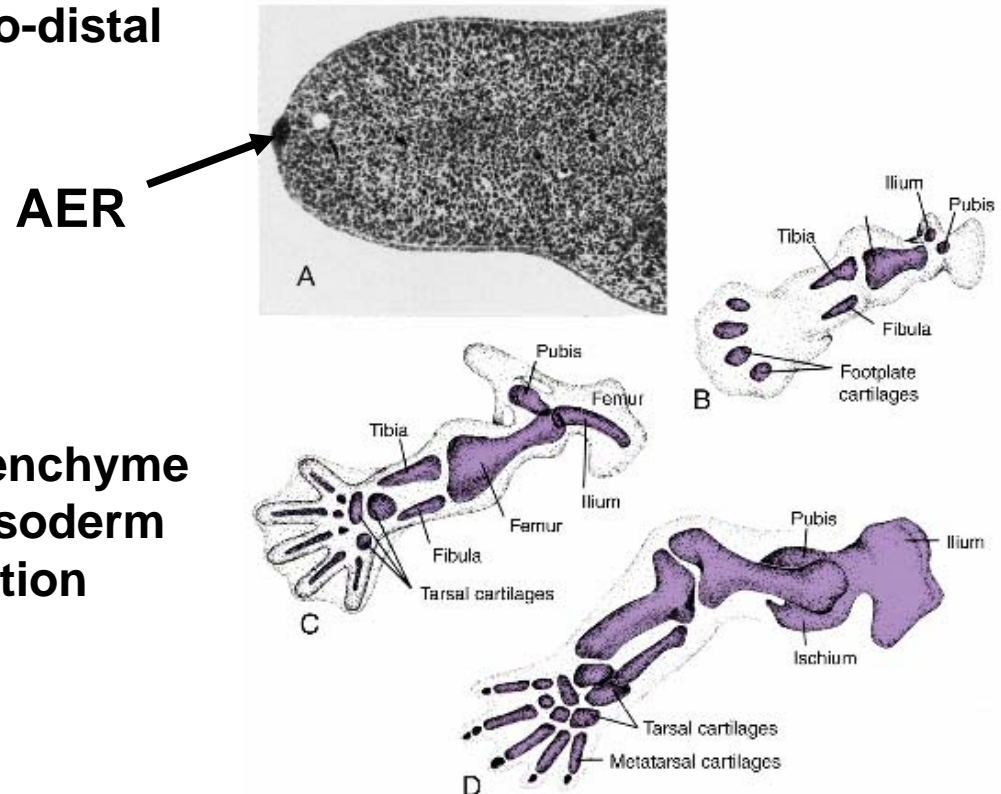


Week 8



Apical ectodermal ridge (AER)

- Forms in ectoderm at distal border of limb bud
- Function = maintains the progress zone which is a region of highly proliferative mesenchyme and inhibits its differentiation
- As AER moves distally, mesenchyme located more proximally undergoes differentiation
- Limb grows proximal-to-distal



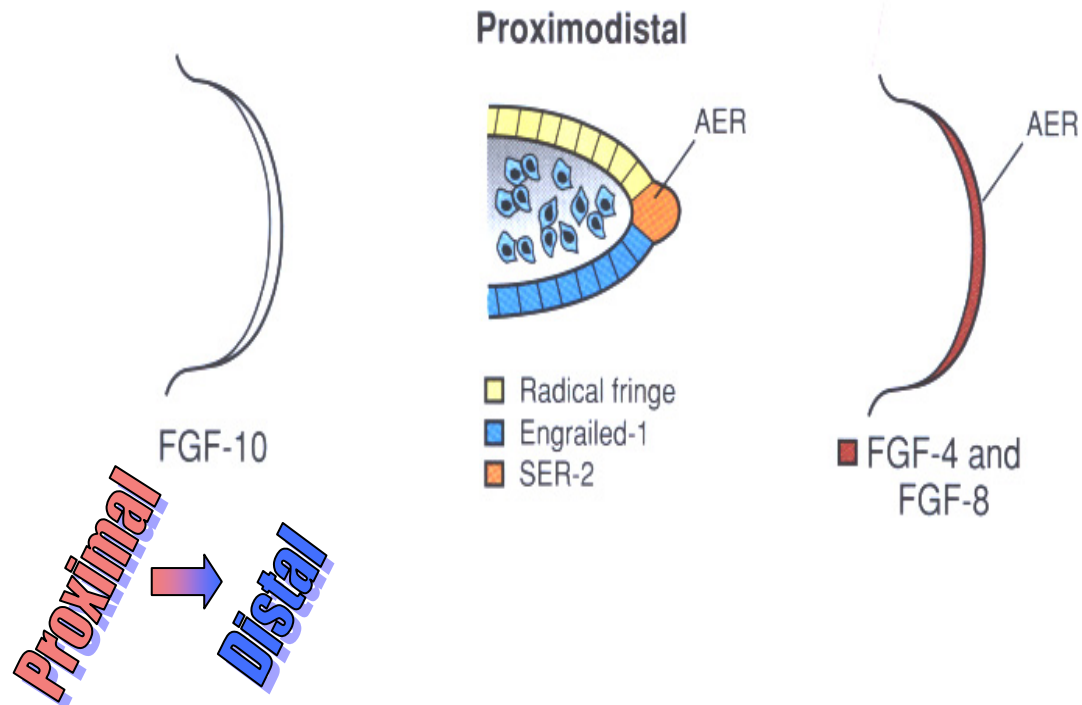
Bone and cartilage

- Differentiate from mesenchyme
- Origin: lateral plate mesoderm
- Endochondrial ossification

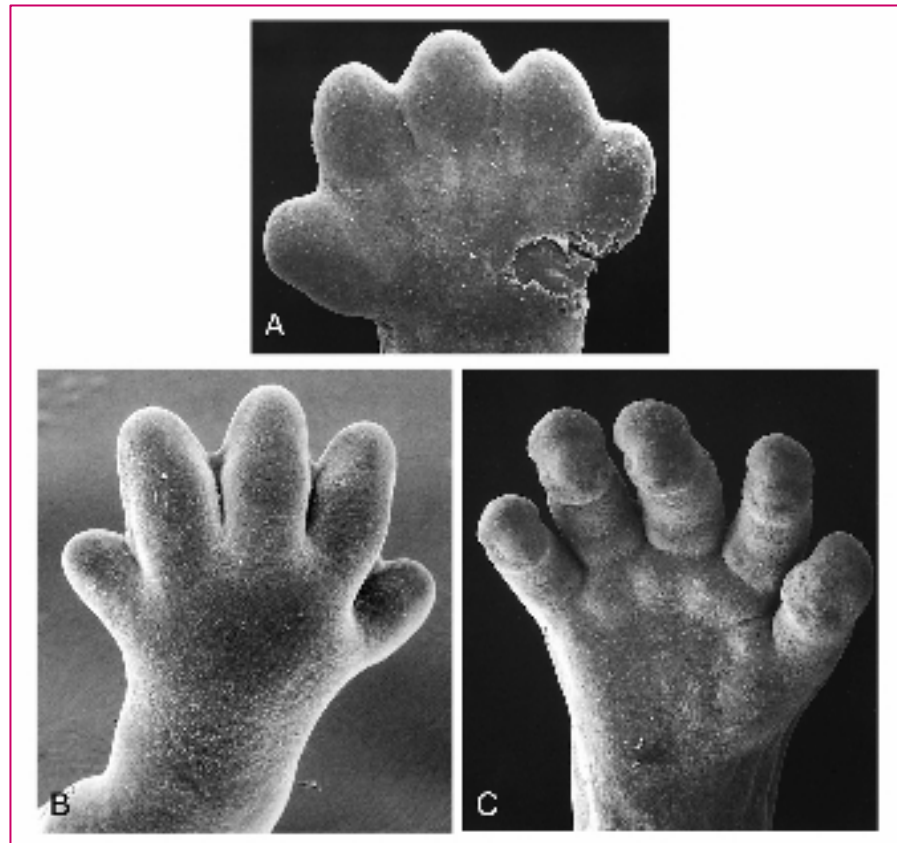
Regulation of Proximal-to-Distal Axis

Temporal Sequence:

- FGF stimulates limb bud outgrowth
- AER formation
 - depends on expression BMPs and Hox genes
 - occurs at border between + and – expression of radical fringe gene
- AER expresses FGF which maintain progress zone



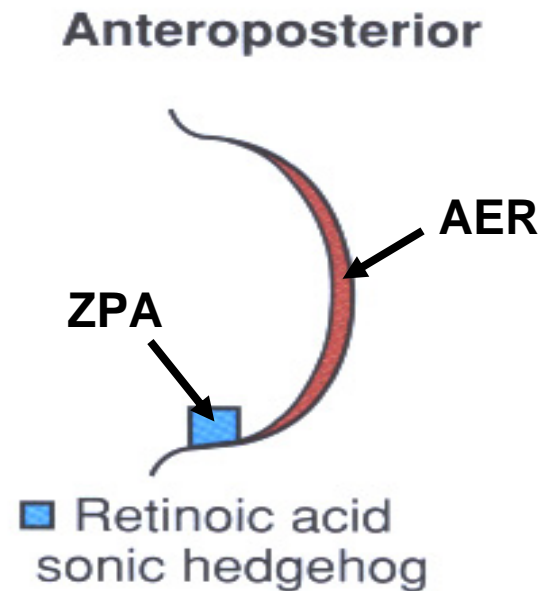
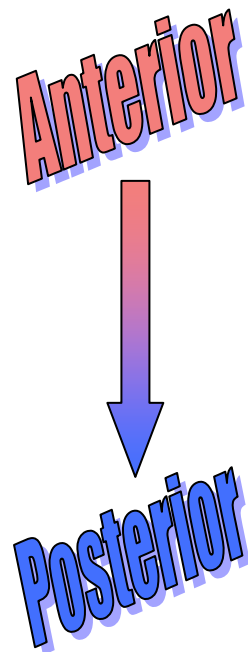
- **Handplates & Footplates Form**
- **Digits defined by programmed cell death in:**
 - **AER at position between outgrowing digits**
 - **Mesenchyme between digits**
- **Circular constrictions define position of joints in digits and limbs**



Regulation of Anterior-to-Posterior Axis

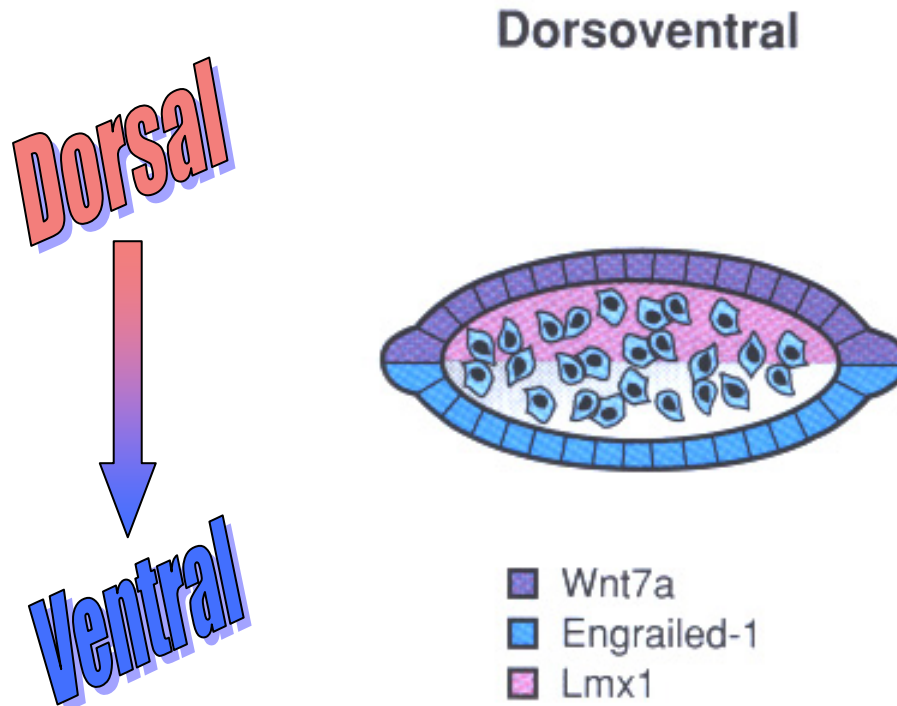
Zone of polarizing Activity (ZPA)

- Located at posterior border of AER
- Moves distally as limb grows
- Expresses retinoic acid (RA) which induces expression of SHH



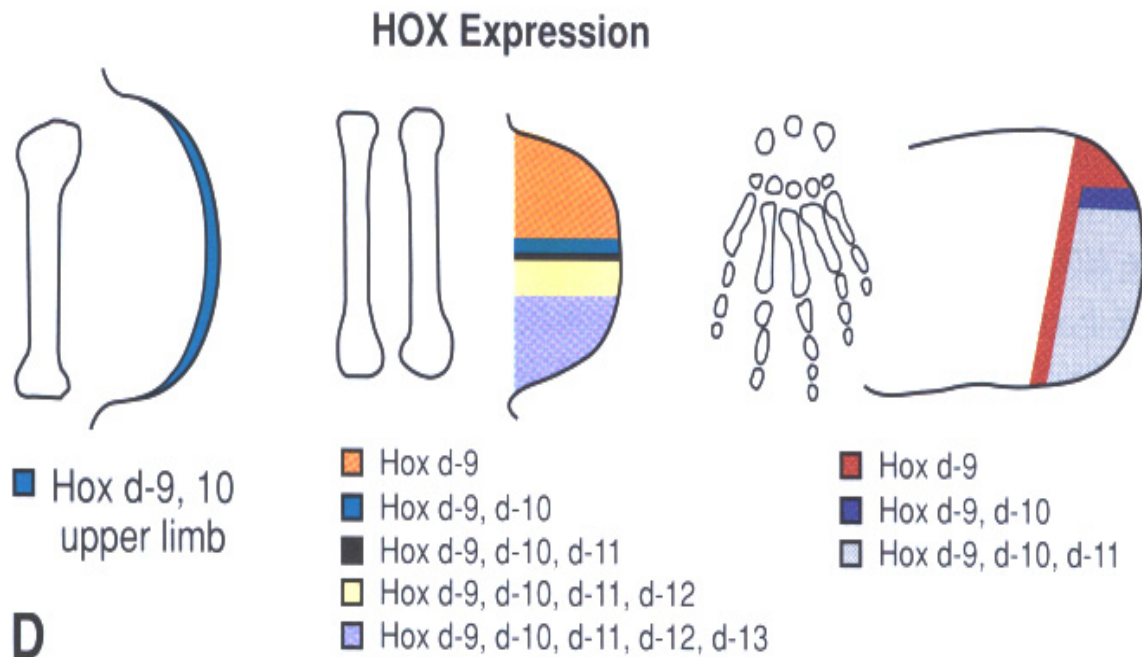
Regulation of Dorsal-to-Ventral Axis

- BMP expression in ventral ectoderm induces expression of Engrailed
- WNT initially expressed in both dorsal and ventral tissue
- Engrailed inhibits WNT expression in ventral mesenchyme
- WNT induces LMX expression in dorsal mesenchyme



Homeobox Genes

- Regulate type and shape of limb bones
- Expression of Hox regulated by SHH, FGFs and WNT
- Dysregulation causes limb and digit malformations

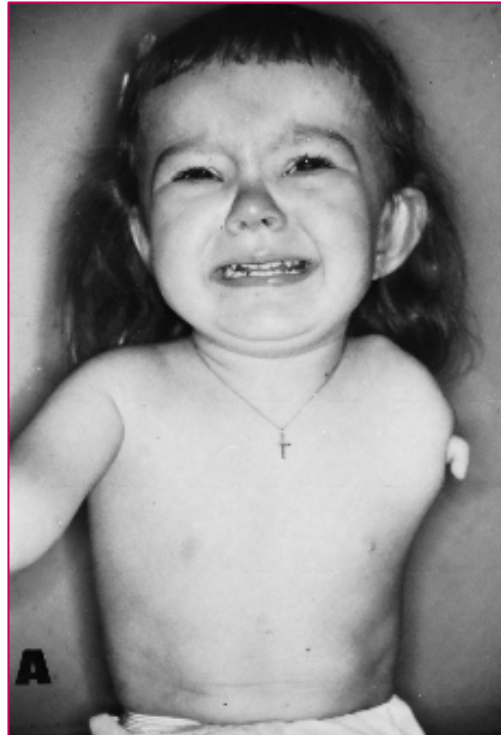


Sirenomelia

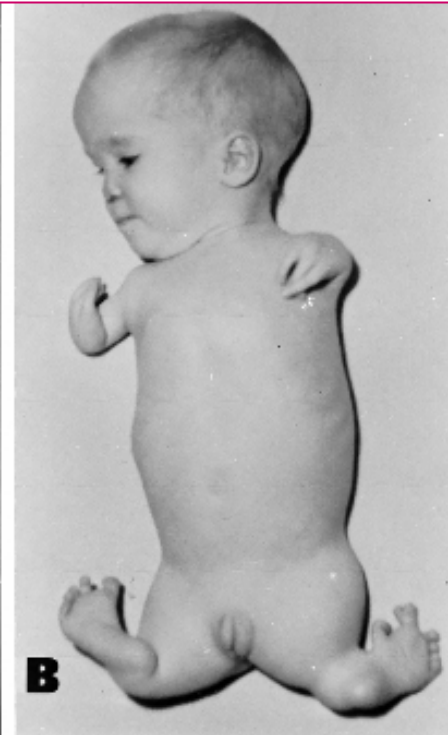


- Caudal dysgenesis
- Defect of gastrulation: lack of mesoderm in caudal region
 - urogenital defects (intermediate mesoderm)
 - vertebral defects (paraxial mesoderm)
 - fusion of hind limb buds (lateral plate mesoderm)
- Causes:
 - genetic
 - teratogens
 - maternal diabetes

Amelia



Meromelia



Etiology:

- Genetic defects
- Thalidomide treatment during pregnancy
 - Anticancer drug
 - Antinausea drug given for morning sickness during 1950s and 1960s

Malformations of Digits

Polydactyly

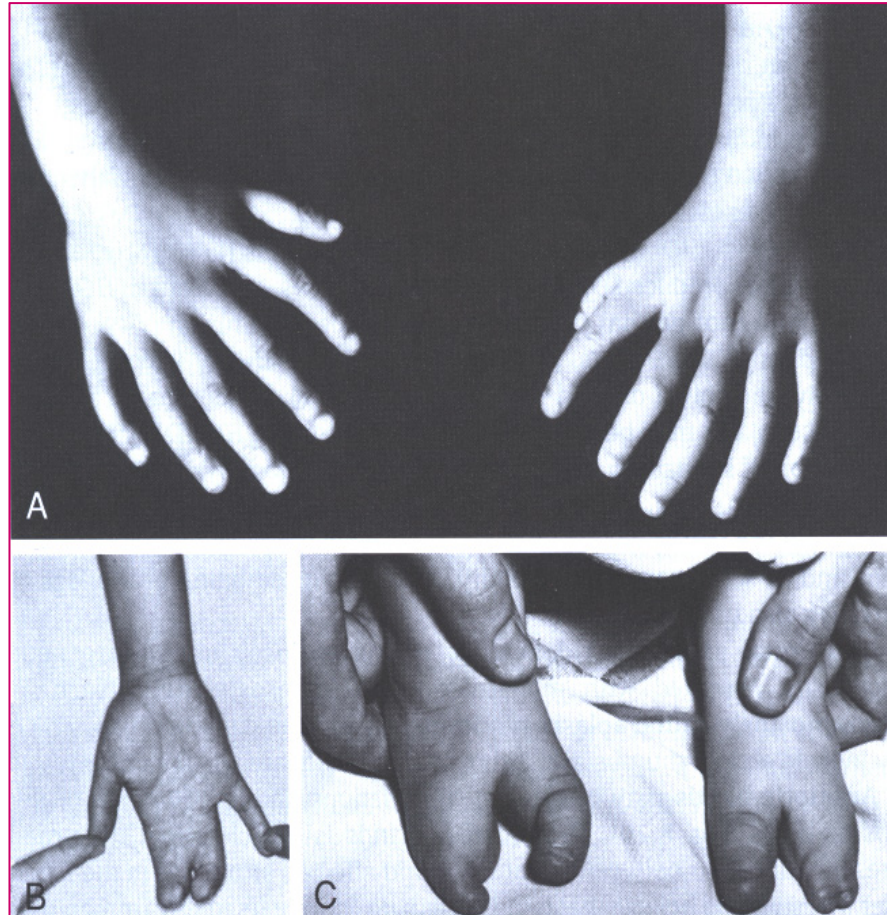
- extra digits

Synpolydactyly (not shown)

- extra digits
- fused digits

Syndactyly

- fused digits
- may be associated with club foot which is adducted and plantar flexed

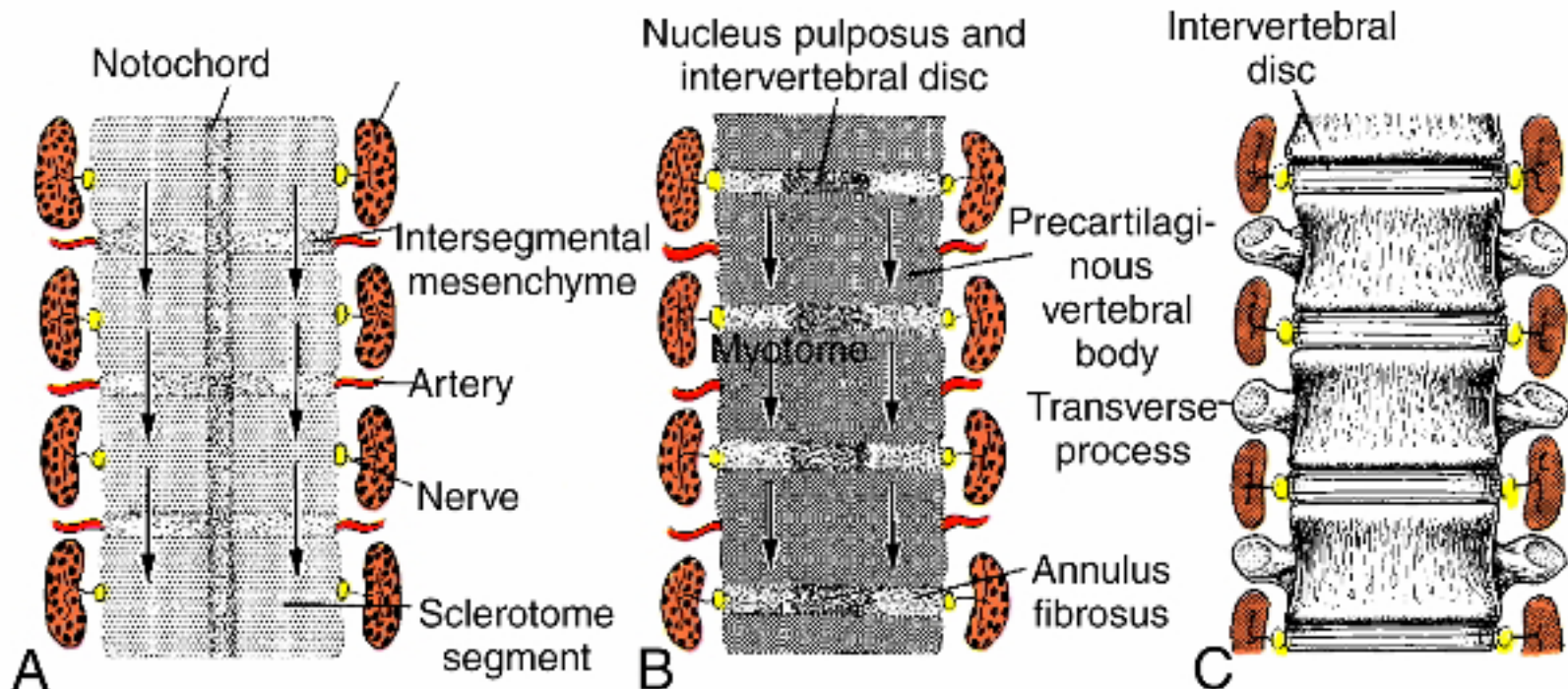


Cleft foot or hand (lobster claw)

- absence of 3rd digit
- fused digits

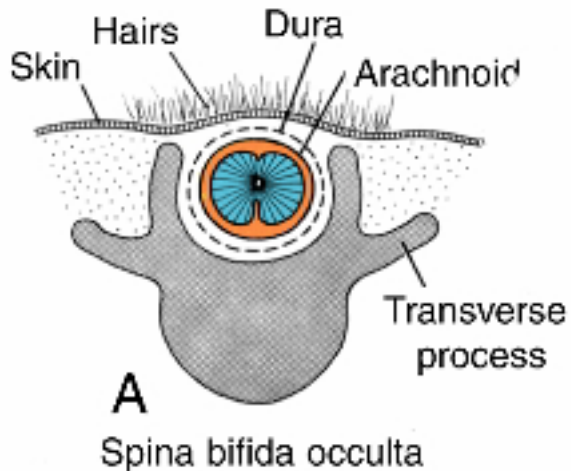
Vertebral Column

- Segmented sclerotome → segmented myotomes with spinal nerves
- Fusion of caudal ½ and cranial ½ of adjacent segments forms vertebral bodies
 - Myotomes bridge the intervertebral discs
 - Spinal nerves exit through intervertebral foramina
 - Intersegmental arteries positioned at level of vertebral body
- Notochord degenerates, except for nucleus pulposus of intervertebral disc

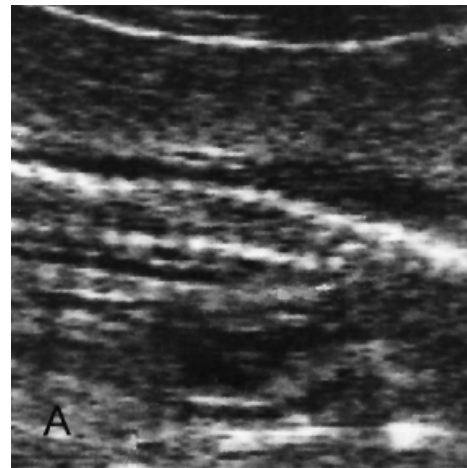


Spina Bifida

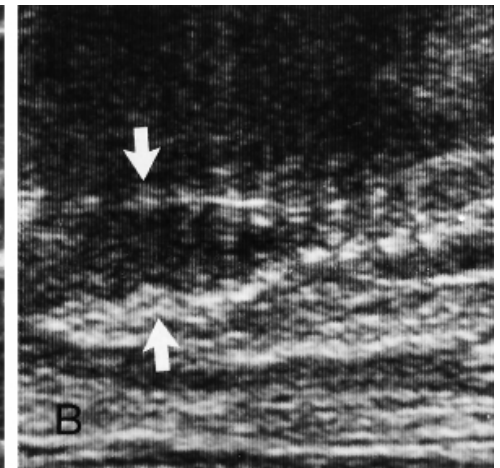
- Neural tube defects (NTD) that affect the spinal region
- Failure to fuse vertebral arches dorsally to surround the spinal cord
- Spina bifida occulta
 - Spinal cord is normal
 - Defect covered by muscle and skin
 - May be tuft of hair overlying defect



Normal Vertebral Column



Spina Bifida
Arrows: cleft vertebra

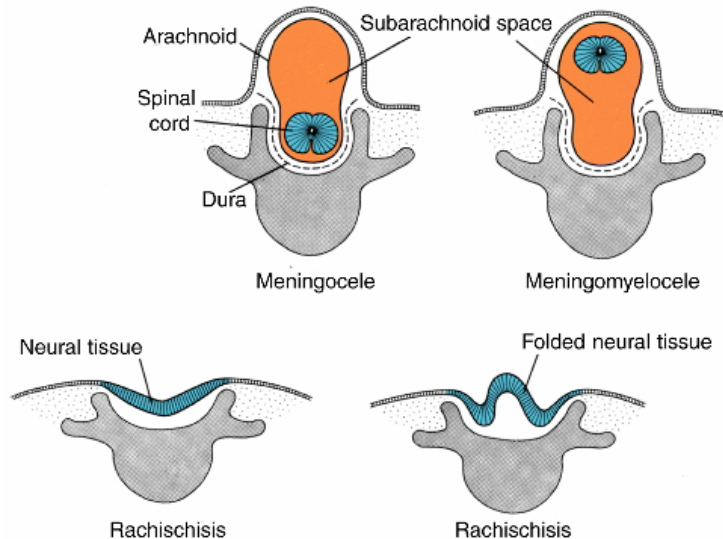


Ultrasound Scan

Spina Bifida

Spina bifida cystica

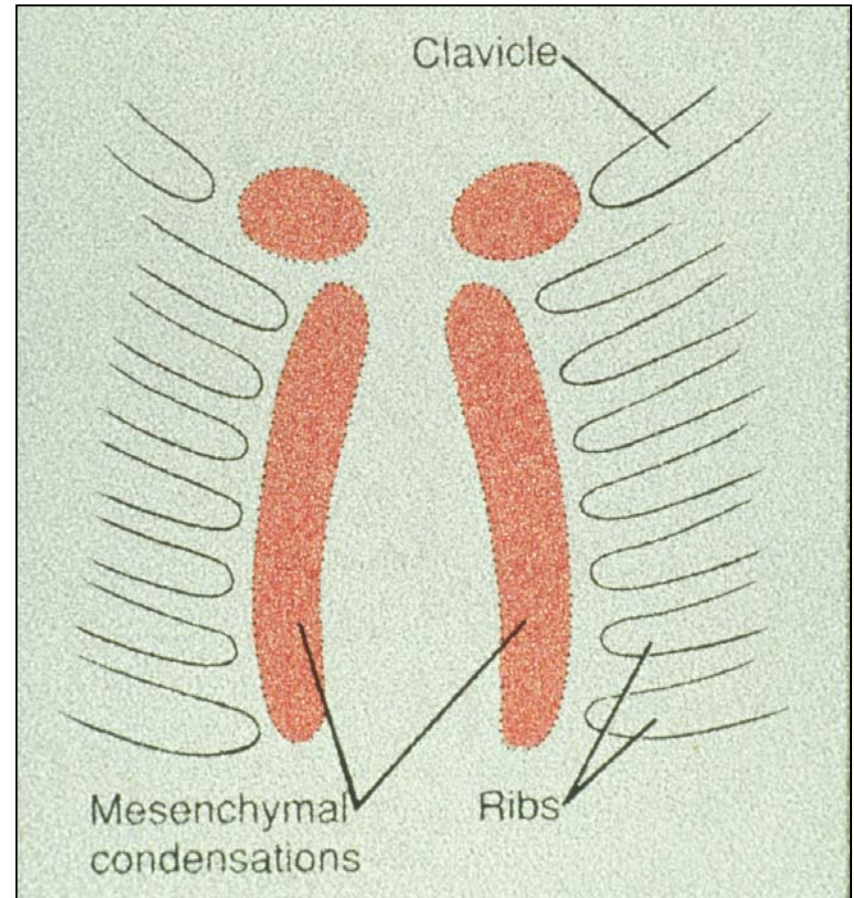
- Caused by failure to fuse neural tube
- Neural tissue and meninges protrude through vertebral defect
 - Meningocele
 - Meningomyelocele
 - Rachischisis
- Associated with neurological deficits
- Commonly involves L4-S1, but may occur at any vertebral level
- Prevention: folic acid supplementation 0.4-1 mg/daily prior to & during pregnancy
- Prenatal diagnosis: elevated α -fetoprotein level in amniotic fluid and maternal serum



Craniorachischisis



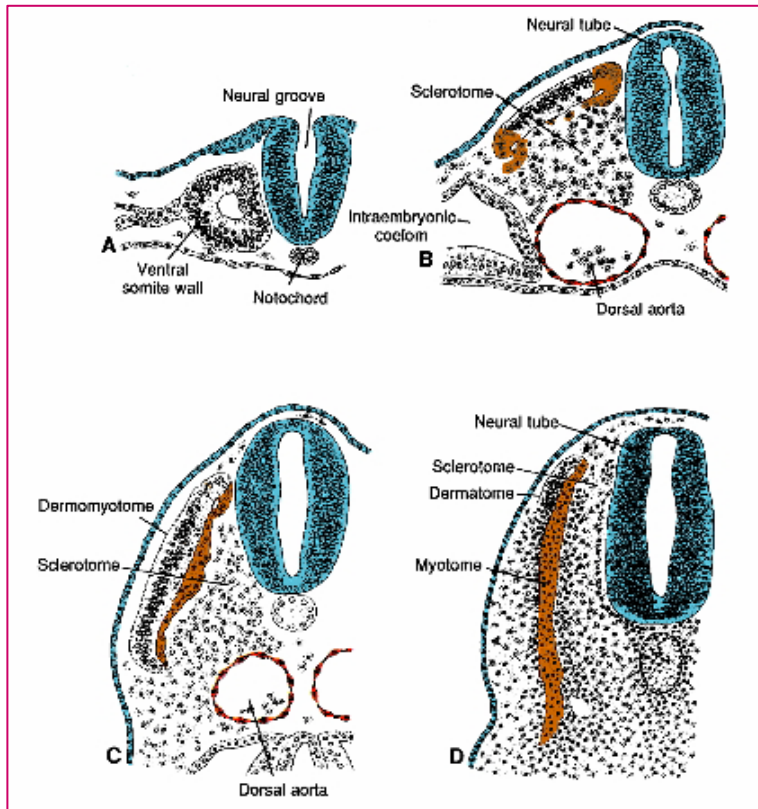
- **Ribs**
 - Arise by growth of costal processes from vertebra
 - Derived from sclerotome
- **Sternum**
 - Fusion occurs at midline
 - Derived from somatic lateral plate mesoderm



Muscular System

Muscle derived from:

- Paraxial mesoderm → Somite → Myotome → Skeletal muscle
- Splanchnic lateral plate mesoderm → Smooth muscle of gut
- Ectoderm → Smooth muscle of integumentary glands
- Splanchnic lateral plate mesoderm → Cardiac muscle



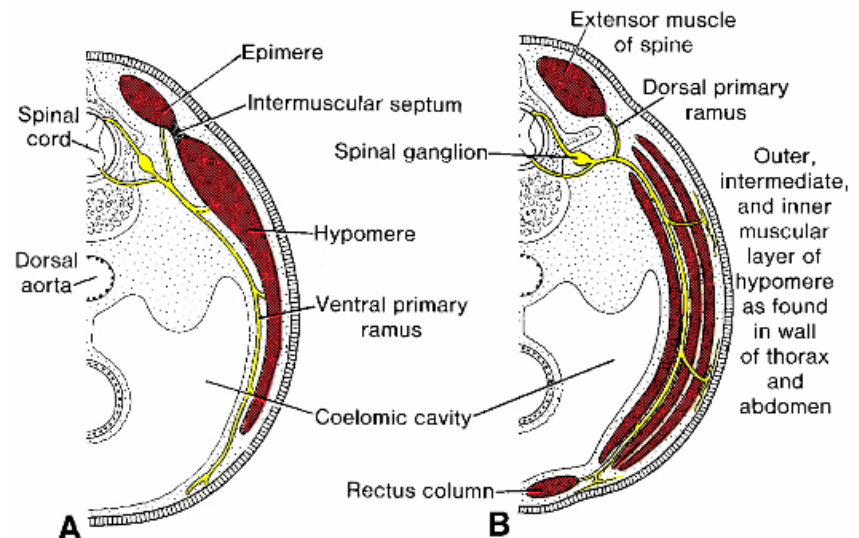
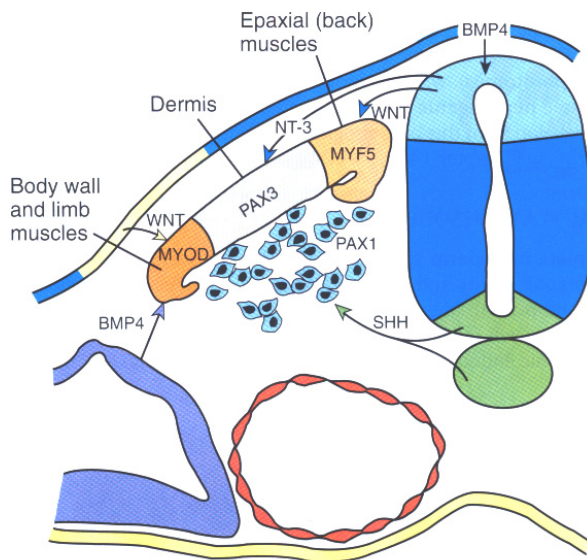
Muscle pattern regulated by connective tissue into which the myoblasts migrate

Connective tissue derived from:

- Head region: neural crest
- Cervical/occipital region: paraxial mesoderm
- Limbs: somatic lateral plate mesoderm
- Body wall: somatic lateral plate mesoderm

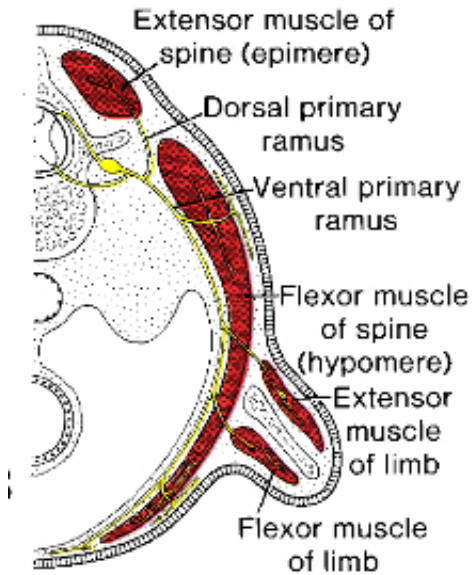
Molecular Regulation of Muscle Development

- Myoblasts differentiate → fuse into multinucleated muscle fibers → myofibrils form in cytoplasm
- MYO-D expression → hypomere → limb and body wall skeletal muscle
 - induced by expression of BMP4 and FGFs from lateral plate
- MYF5 expression → epimere → extensor muscles of axial skeleton
 - BMP4 expression by ectoderm induces dorsal neural tube expression of WNT, which induces MYF5 expression
 - MYO-D and MYF5 induce expression of myogenin and MRF5 involved in formation of myotubes and myofibers

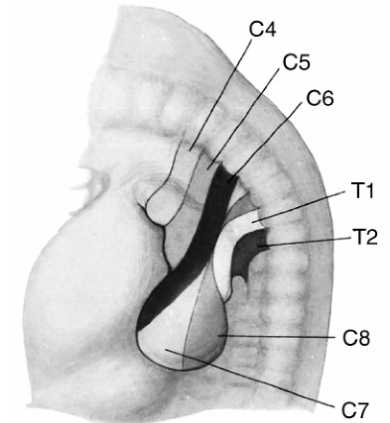
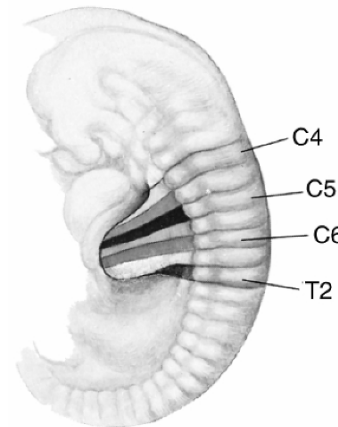


Note: innervation of hypomere and epimere

Limb Musculature



- Flexor and extensor muscles derived from hypomere
- Innervated by ventral primary rami



Myotome and Dermatome Patterns

- Innervation of segments lying lateral to spinal nerves
- Myotomes fuse and merge during migration to form large muscles
- Dermatomes remain segmented in adult
- Limb rotation alters pattern
 - upper: 90° laterally (elbow posterior)
 - lower: 90° medially (knee anterior)

