Lecture - Musculoskeletal Development

Introduction

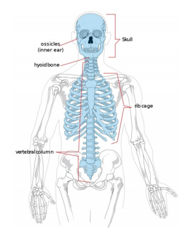
This lecture is an introduction to the process of musculoskeletal development (bone and skeletal muscle) (b. In the body, this is mainly about **mesoderm** differentiation beginning with an embryonic connective tissue structure, the **mesenchyme**.

In the head, this is a mixture of mesoderm and neural crest differentiation, from mesenchyme and ectomesenchyme respectively. The lecture will cover mainly cartilage and bone, as muscle will be covered in the limb lecture and in this week's laboratory.

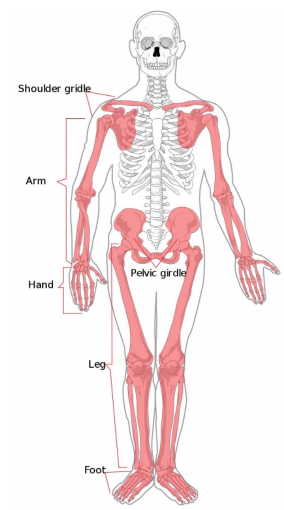
The **axial** and the **appendicular** skeleton.

- axial skeleton - 80 bones (skull, vertebrae, ribs, and sternum)
- appendicular skeleton - 126 bones (shoulders, pelvis, and limbs)

Note that genes that control skeleton patterning and cell differentiation are different.



Axial skeleton

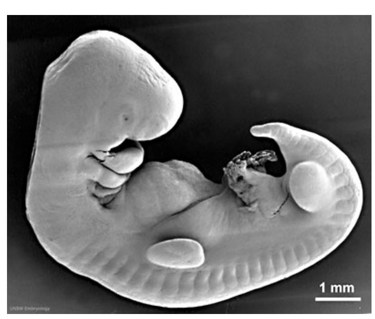


Appendicular skeleton

2016 Lecture Video Recording [Expand]

Lecture Objectives

- Understanding of mesoderm and neural crest development.
- Brief understanding of connective tissue development.
- Understanding of cartilage, bone and muscle development.
- Understanding of the two forms of bone development.
- Brief understanding of molecular bone development.
- Brief understanding of bone



Week 5 Embryo showing somites.

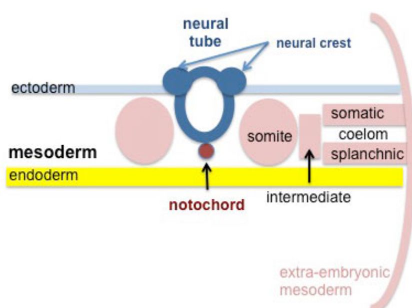
Week 9.5 Fetus showing bone

abnormalities.		formation.

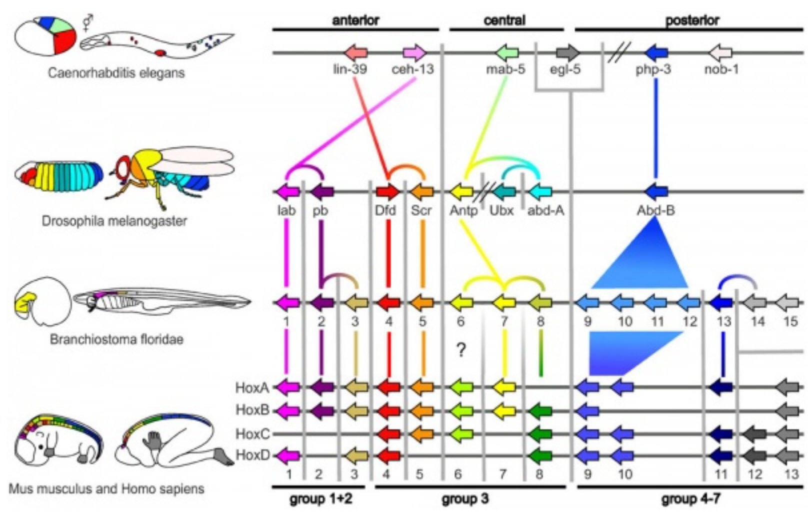
Lecture Resources

Movies	[Expand]
References	[Expand]

Patterning and differentiation of the somitic mesoderm



- Week 3 to 4 - **paraxial mesoderm** forms **somites** (somitogenesis) along the rostro-caudal axis establishes the axial body plan
  - paraxial mesoderm remains unsegmented in the head
- **Hox** gene clusters control rostro-caudal patterning of the axial musculoskeletal system
  - provide positional clues for the development of specific structures e.g. cervical, thoracic, lumbar and sacral vertebrae.



Somite Patterning

Neural Crest Derived Cells

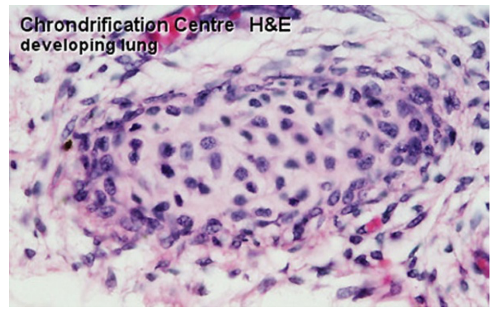
(see Neural Crest and Head Lectures)

- Neural crest-derived cells are essential to form the bones and cartilage of the face and neck
- Also forms the cranial nerves and pigment cells, dorsal root ganglia and the sympathetic neurons.

Cartilage Development

Most of the skeleton is formed initially by cartilage that is then replaced by bone

-
    - described as a "cartilage template" for ossification (endochondral ossification)
    - except for joint surfaces - hyaline cartilage
- Hyaline cartilage develops from mesenchymal cells, forming chondrification centres.
- chondroblasts secrete ECM components of matrix, that separates them into lacunae.



chondrification centre

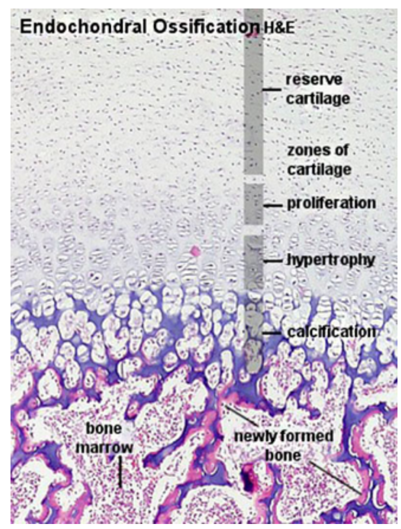
Cartilage 3 stages:

1. Signalling interactions between mesenchyme and an epithelial population
2. Cell Condensation - mesenchymal dispersed cell population, gathers together to differentiate
3. Overt Differentiation

Cartilage replacement

- periosteal bud invades the cartilage and allows **osteoprogenitor cells** to enter the cartilage.
    - blood vessel growth and osteoprogenitor cells attracted by growth factors released from dying chondrocytes.

Cartilage Template [Expand]



Endochondral ossification

Cartilage Growth

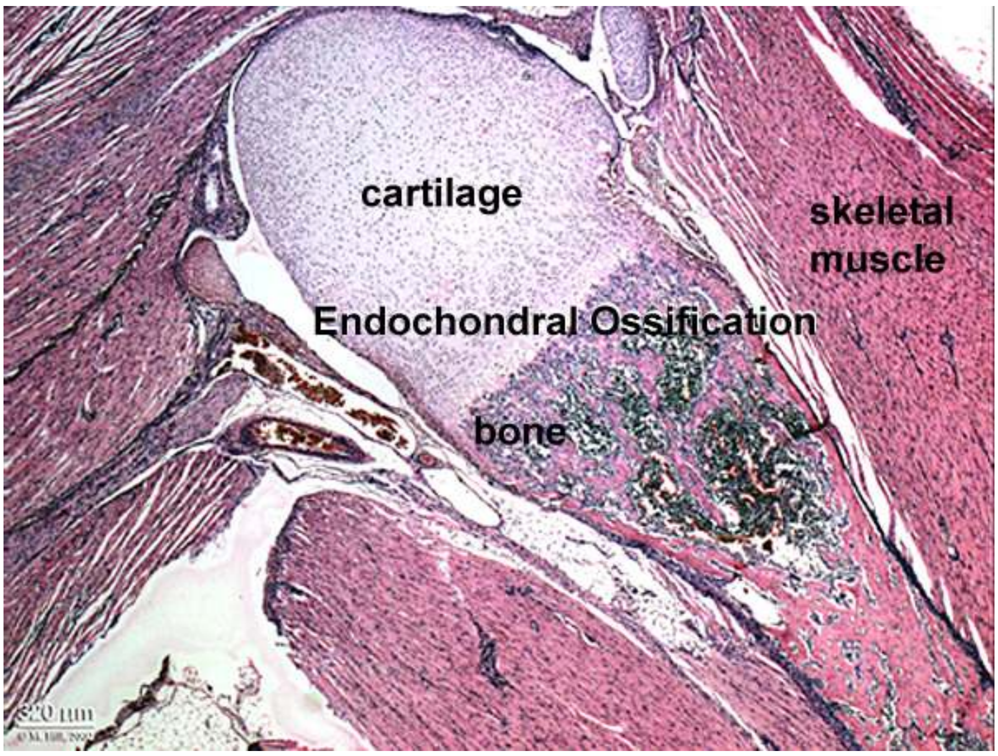
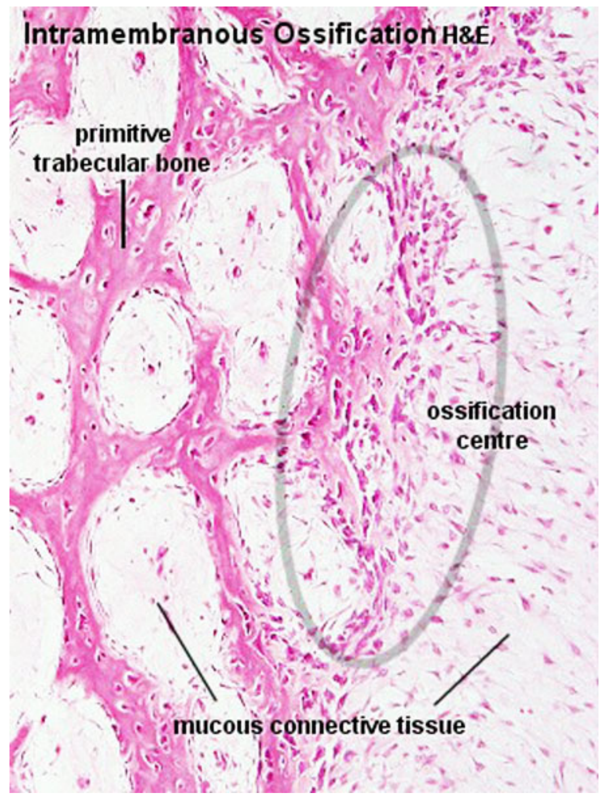
- **Interstitial growth** - occurs mainly in immature cartilage. Chondroblasts in existing cartilage divide and form small groups of cells (isogenous groups) which produce matrix to become separated from each other by a thin partition of matrix.
- **Appositional growth** - occurs also in mature cartilage. Mesenchymal cells surrounding the cartilage in the deep part of the perichondrium (or the chondrogenic layer) differentiate into chondroblasts.

(review your Histology materials)

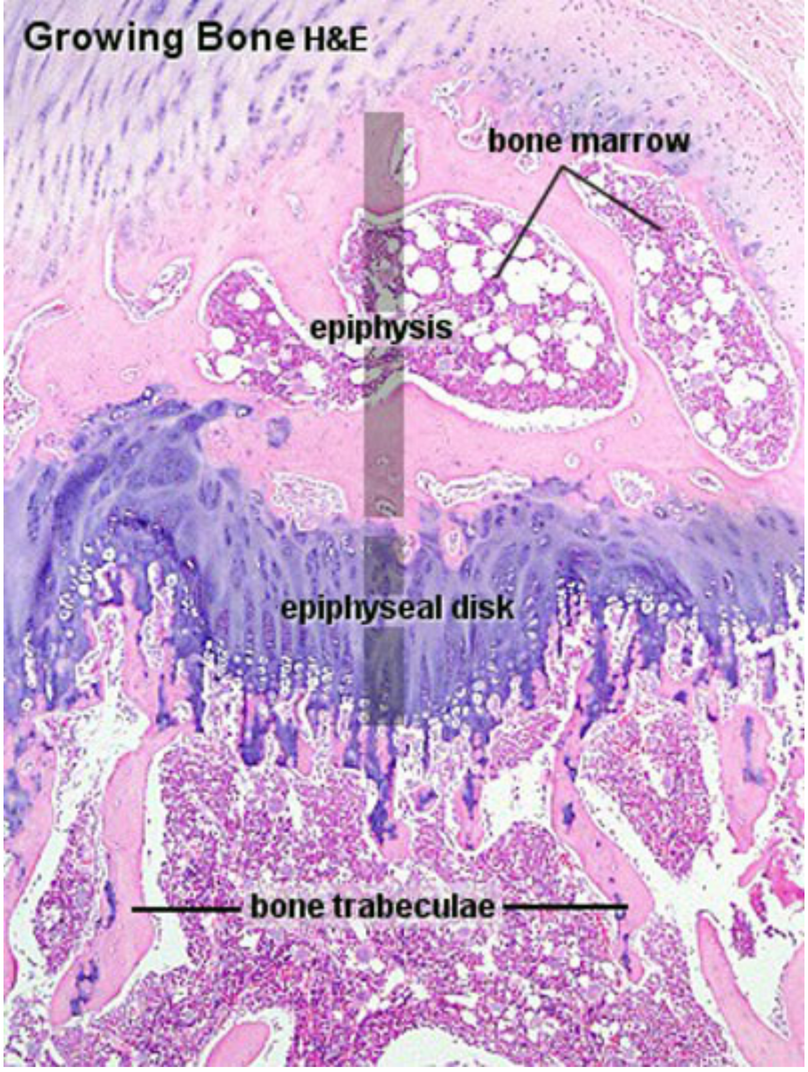
Hypertrophic Chondrocytes

- secrete VEGF, promoting vascular invasion
- hypertrophic calcified cartilage becomes resorbed, by recruited chondroclasts/osteoclasts via MMP9

Formation of Bone

	
Endochondral primary ossification centres	Intramembranous ossification centres

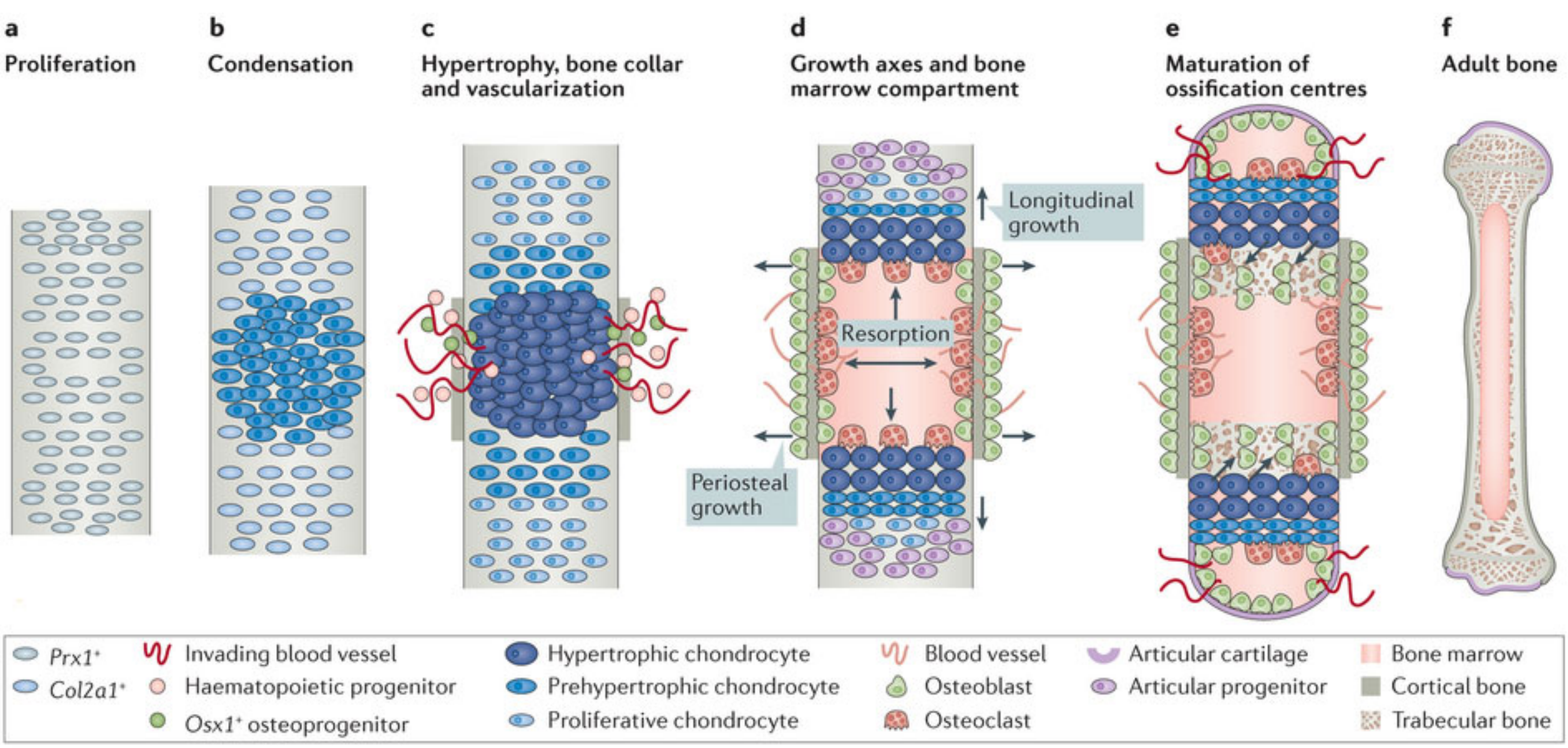
- Two main forms of bone formation: Endochondral and Intramembranous.
- Ossification process continues postnatally through puberty until mid 20s.



Endochondral initial primary and later secondary ossification centres ([sites cartoon](#)

Periosteum is the source of osteoprogeitors for later bone growth

Endochondral Ossification



PMID 26893264 Nature Reviews | Endocrinology

Endochondral Ossification[1]

- Majority of skeleton formed by this process (vertebra, limb long

bones)
- Osteoblasts derived from the bone collar replace cartilage matrix with a matrix rich in type I collagen leading to bone formation
- Ossification centres (primary and secondary)
- Early ossification occurs at ends of long bone

- Diagram of ossification in long bone University of Bristol - ossification

Endochondral bone development - Role of VEGF

Development of Vertebrae

Limb Bone Timeline [Expand]

Links: Bone Development Timeline | primary and secondary sites | Mice lacking Cbfa1 (Runx2) don't form bone

Vertebral segmentation

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- shifted 1/2 somite caudally - by fusion rostral compact with caudal loose to form vertebra from 2 sclerotomes allows

1. segmental spinal nerves to emerge between the vertebral bodies (at the same level as the intervertebral discs)
2. somite-derived muscle masses to interconnect between the intervertebral joints.

Adult vertebral column

- 33 total - 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 5 coccygeal

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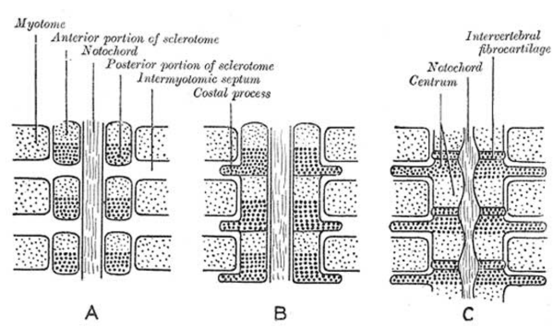

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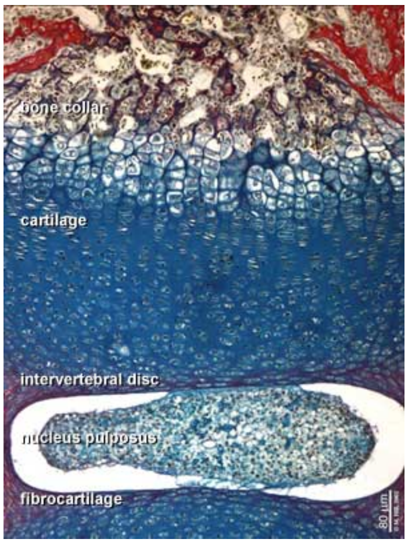
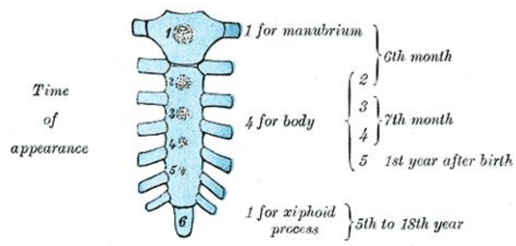
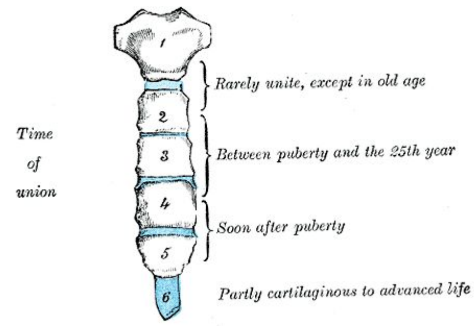
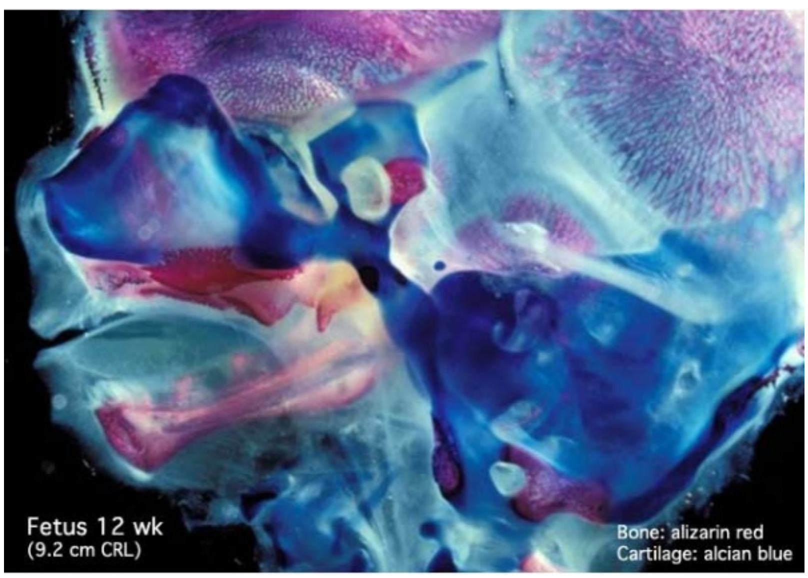
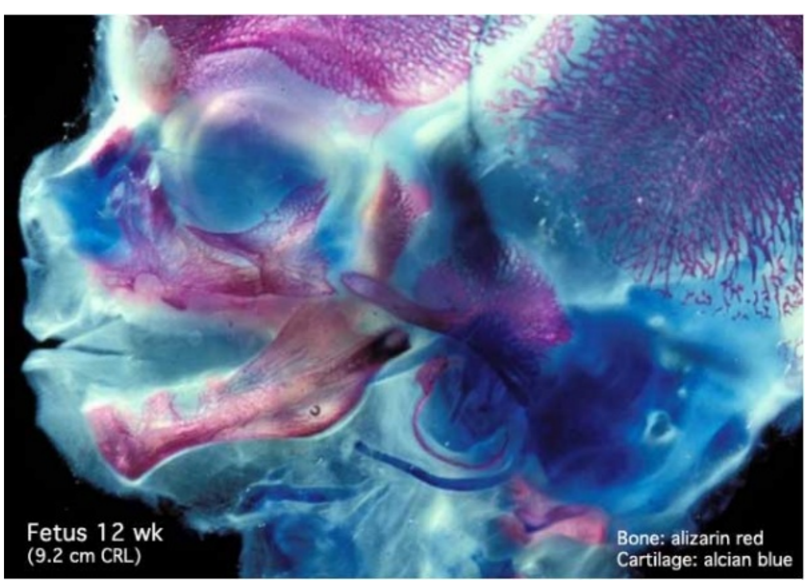
Axial Elements

Intervertebral Disc	Ribs	Sternum
Structure - annulus and nucleus pulposus	vertebra origin: body, arch, and costal process	• mesenchyme

• dense region of sclerotome. • notochord initially contributes to nucleus pulposus of each disc, contribution replaced and lost postnatally.  	• dense region of sclerotome contributes costal processes (thoracic region). ◦ chondrification commences day 45 and rib cage is cartilage by end of embryonic period.  Ossification of the sternum.	from ventral body wall (manubrium, body, ziphoid). • sternal cartilage "bars" fuse with costal processes and developing clavicles by end of embryonic period. 

Intramembranous Ossification

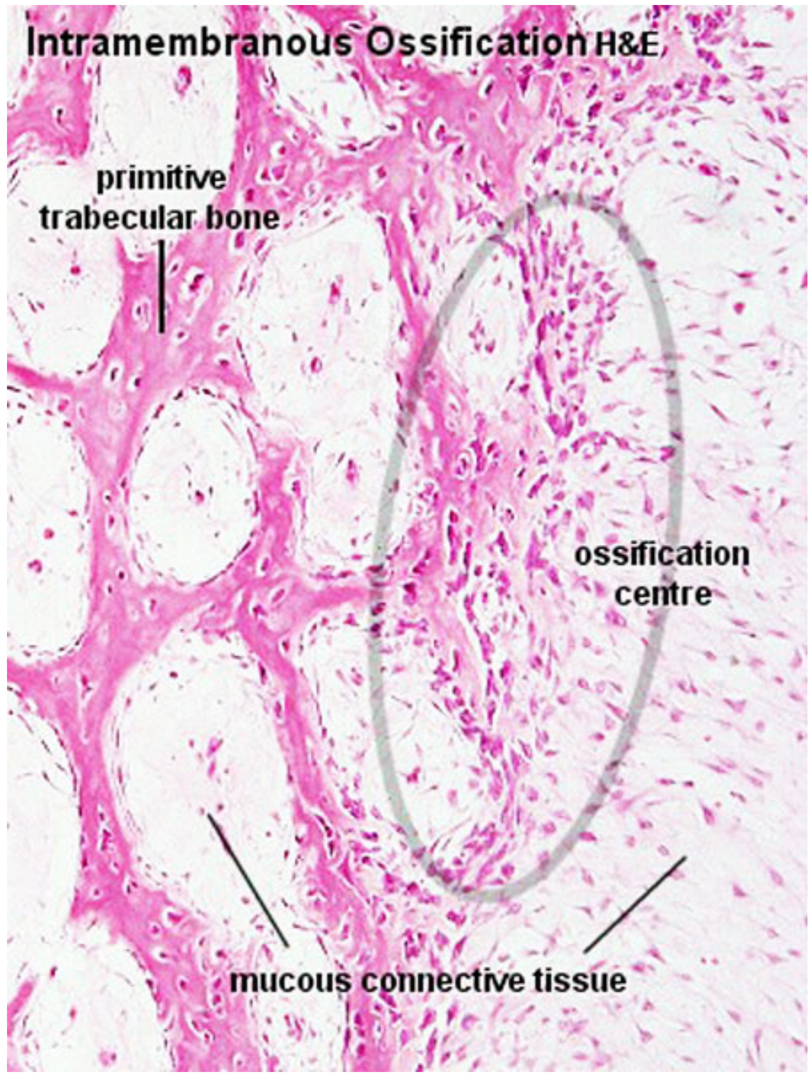




- Specialized form of ossification from a mesenchymal membrane. (skull and clavicle)

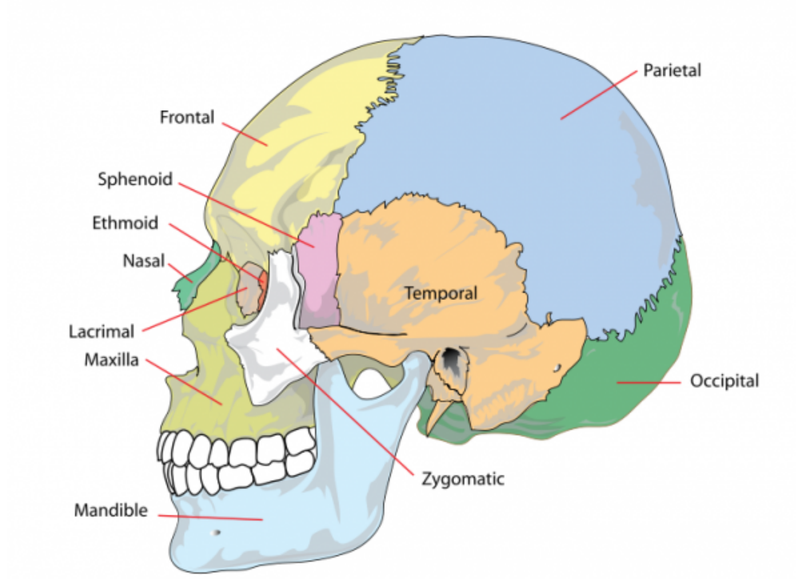
- Neural crest-derived mesenchymal cells proliferate - some cells differentiate to form blood vessels, others become osteoblasts and begin secreting collagen-proteoglycan matrix that can bind calcium salts.
- Initial mesenchyme condensation is avascular.
- Angiogenesis is then required for intramembranous osteogenesis (vessels provide circulating factors)

  Links: - Intramembranous ossification

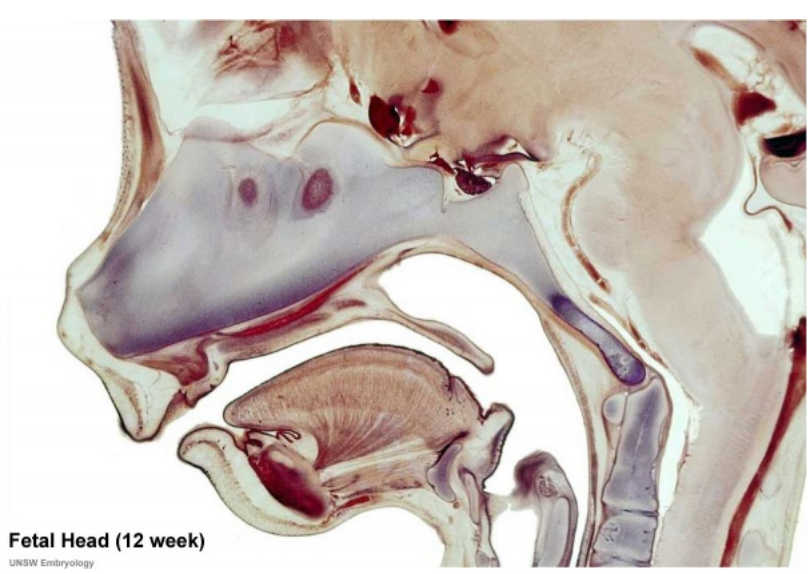


Skull

The Skull is a unique skeletal structure in several ways: embryonic cellular origin (neural crest), form of ossification (intramembranous and endochondrial) and flexibility (fibrous sutures). Musculoskeletal Development - Skull Development



The bones enclosing the brain have large flexible fibrous joints (sutures) which allow firstly the head to compress and pass through the birth canal and secondly to postnatally expand for brain growth.



These sutures gradually fuse at different times postnatally, firstly the metopic suture in infancy and the others much later. Abnormal fusion (synostosis) of any of the sutures will lead to a number of different skull defects.

Osteogenesis

- Osteoprogenitor cell - periosteum and endosteum
- Osteoblast - Secrete bone matrix, differentiate into osteocytes
- Osteocyte - Mature bone cell, Embedded in matrix, matrix calcifies soon after deposition

Blood and Stromal Stem Cells [Expand]

Osteoclastogenesis

- Formation of mature osteoclasts involved in bone resorption - the osteoblasts regulate this process through the production of RANKL (Receptor Activator for Nuclear Factor κ B Ligand) which is found on the cell surface of osteoblasts.
- RANKL is a key player in rheumatoid arthritis.
- Osteoclast origin - fusion of monocytes or macrophages, Blood macrophage precursor
- Attach to bone matrix - very large cells containing 15-20 nucleii.
- Lysosomes - released into space between ruffled border and bone matrix, enzymes break down collagen fibres, resorption bays or Howship's lacunae

Muscle

Myogenesis

(This lecture is about skeletal muscle)

- **Skeletal muscle** - cells originate from the paraxial mesoderm. Myoblasts undergo frequent divisions and coalesce with the formation of a multinucleated, syncytial muscle fibre or myotube. The nuclei of the myotube are still located centrally in the muscle fibre. In the course of the synthesis of the myofilaments/myofibrils, the nuclei are gradually displaced to the periphery of the cell.

- **Cardiac muscle** - cells originate from the prechordal splanchnic mesoderm.

- **Smooth muscle** - cells originate from undifferentiated mesenchymal cells. These cells differentiate first into mitotically active cells, myoblasts, which contain a few myofilaments. Myoblasts give rise to the cells which will differentiate into mature smooth muscle cells.

Skeletal Muscle Stages

specified cells	myoblasts	primary myotube	secondary myotube	myofibre
somite myotome	migration to muscle location and proliferation	initial myoblast fusion	later myoblast proliferation and fusion	innervation and expression of contractile proteins

1. **Myoblast** - individual progenitor cells (from myotome)
2. **Myotube** - multinucleated, but undifferentiated contractile apparatus (sarcomere)
3. **Myofibre** (myofiber, muscle cell) - multinucleated and differentiated sarcomeres
    1. primary myofibres - first-formed myofibres, act as a structural framework upon which myoblasts proliferate, fuse in linear sequence
    2. secondary myofibers - second later population of myofibres that form surrounding the primary fibres.

Mouse muscle development [Expand]

Muscle Fibre Types

- Motor neuron will regulate the contractile properties of all associated myofibres.

    - A group of individual myofibres within a muscle will be innervated by a single motor neuron.
- myosin ATPase activity determines - type IIB, IIA, IIX, and I fibres
    - Type I fibres - appear red, due to the presence of myoglobin (main type in fetal life)
    - Type II fibres - appear white, due to the absence of myoglobin and their glycolytic nature.

Muscle fibre type table [Expand]

Myotome

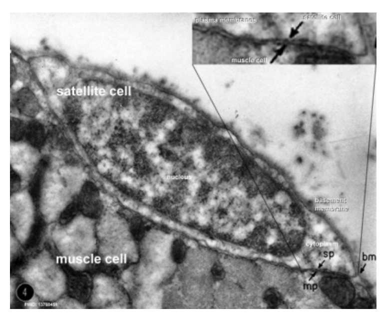
This term is used to describe the region of the somite that contributes skeletal muscle to the embryo body. Each somite pair level gives rise to a group of skeletal muscles supplied by a specific segmental spinal nerve. The muscle arises from a specific somite and the spinal nerve arises from a specific level of the spinal cord (identified by vertebral column).

Spinal Nerve Table [Expand]

Satellite Cells

Muscle stem cells located under the basal lamina around each skeletal muscle fibre.

- They have a role in postnatal growth and also regeneration of muscle fibres.



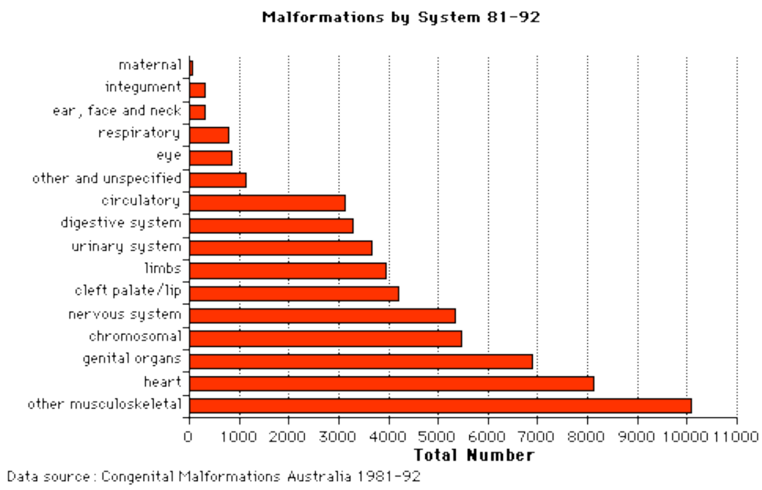
Puberty

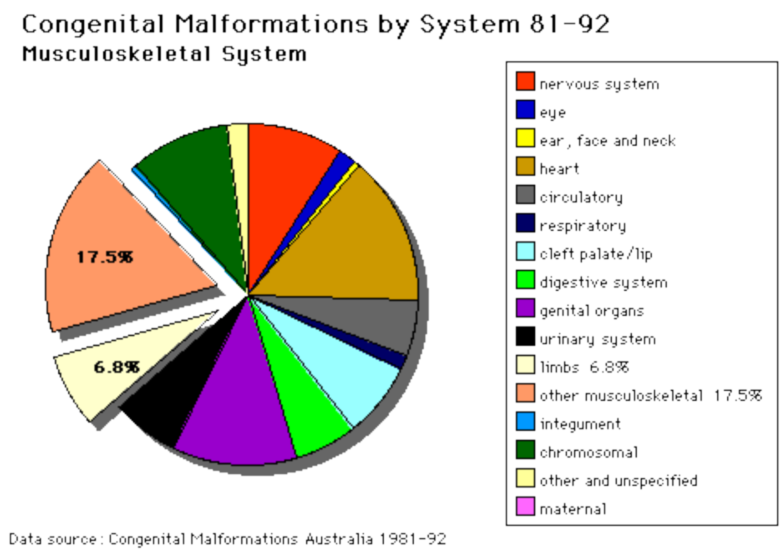
- Musculoskeletal mass doubles by the end of puberty
- regulated growth by - sex steroid hormones, growth hormone, insulin-like growth factors
- accumulation of (peak) bone mass during puberty relates to future osteoporosis in old age

Abnormalities

Additional abnormalities will be covered in the limb development lecture.

> "Arthritis and musculoskeletal conditions affect more than 6 million Australians. In 2004-05, direct health expenditure on these conditions amounted to $4.0 billion or 7.5% of total allocated health expenditure in Australia." Health expenditure for arthritis and musculoskeletal conditions, 2004-05





Bone

Vertebra

- Spina Bifida - neural tube failure to close, disrupts neural arch formation
- Block vertebra - failure of vertebra separation, lumbar region, chrondrification abnormality
- Klippel-Feil Syndrome - non-segmented cervical vertebra, more female
- see also scoliosis

Rib

- Accessory rib (extra rib cervical or lumbar uni- or bilateral), short-rib polydactyly syndrome (lethal, chondroplasia), pigeon chest (rib overgrowth), funnel chest (sternum depression and lower costal cartilages)

Osteogenesis Imperfecta

- brittle-bone syndrome
- abnormal collagen type I, fail to assemble triple helix, degrade imperfect collagen, leads to fragile bones

Scoliosis

- assymetric growth impairment of vertebral bodies
- lateral deviation of spine (Lateral flexion, Forward flexion, Rotation of vertebral column on long axis)
- compensated by movement of vertebral column above and below affected region (producing a primary and two secondary curves)
- progresses rapidly in adolescence and becomes fixed once bone growth is completed.

Congenital Hip Dislocation

Congenital Hip Dislocation

- Instability: 1:60 at birth; 1:240 at 1 wk: Dislocation untreated; 1:700
- congenital instability of hip, later dislocates by muscle pulls or gravity
- familial predisposition female predominance
- Growth of femoral head, acetabulum and innominate bone are delayed until the femoral head fits firmly into the acetabulum

Muscle

MH - Covered in next lecture and lab.

- Congenital Myopathies
- Muscular Dystrophy

References

1. ↑ Valerie S Salazar, Laura W Gamer, Vicki Rosen **BMP signalling in skeletal development, disease and repair.** Nat Rev Endocrinol: 2016; PubMed 26893264
2. ↑ Leila Taher, Nicole M Collette, Deepa Murugesh, Evan Maxwell, Ivan Ovcharenko, Gabriela G Loots **Global gene expression analysis of murine limb development.** PLoS ONE: 2011,

6(12);e28358 PubMed 22174793 | PMC3235105 | PLoS One.

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Paraxial and intermediate mesoderm | Myogenesis: The Development of Muscle | Osteogenesis: The Development of Bones | Figure 14.10. Conversion of myoblasts into muscles in culture

- **Molecular Biology of the Cell** Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 Search Molecular Biology of the CellBone Is Continually Remodeled by the Cells Within ItImage: Figure 22-52. Deposition of bone matrix by osteoblasts.Image: Figure 22-56. The development of a long bone.

Search

- **Bookshelf** mesoderm | somite | myogenesis | chondrogenesis | osteogenesis
- **Pubmed** mesoderm | somite | myogenesis | chondrogenesis | osteogenesis

External Links

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- **UWA Blue Histology** Skeletal Tissues - Muscle | Skeletal Tissues - Cartilage | Skeletal Tissues - Bone
- **University of Kansas Histoweb** Bone

- **Loyola University Medical Education Network** Part 9: Specialized Connective Tissue: Cartilage and Bone | Part 10: Endochondral Ossification
- **University of Bristol** ossification

Terms

Bone Terms	[Expand]

Images

- Hox and vertebral ossification sequence
- Bone remodeling cycle

2017 ANAT2341 - Timetable | Course Outline | Group Projects | Moodle | Tutorial 1 | Tutorial 2 | Tutorial 3
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Student Projects: 1 Cortex | 2 Kidney | 3 Heart | 4 Eye | 5 Lung | 6 Cerebellum