Embryology; Development and Growth of the Limbs

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Limb elements arise from paraxial mesoderm (somites) and parietal layer of the lateral plate mesoderm.

From paraxial mesoderm (somites):
- **Dermatome**: gives rise to connective tissue of the dermis
- **Myotome**: gives rise to limb muscles

From parietal layer of the lateral plate mesoderm:
- Bones, Blood vessels and connective tissue are developed

The motor innervation: originates from the spinal cord; the myelinating glia (Schwann cells), are from the neural crest.

The upper limb is formed at segmental levels C5-C8 and T1. The lower limb is at L2-L5 and S1,2,3 segmental level.
Limb buds appear at the end of the 4th week of development. They become visible as an outpocketings on the ventrolateral body wall. The upper limbs appear first followed by the lower limb 1 to 2 days later. The limb bud consists of mesenchymal tissue covered by cuboidal cells of the Ectoderm.
The Ectodermal layer at the apical region of the limb bud thickens and forms the **Apical Ectodermal Ridge (AER)**. That ridge stimulates the underlying mesodermal mesenchyme to become rapidly proliferating and is now called the **progress zone**. The presence of the **Apical Ectodermal Ridge** is essential for the proliferation of the mesenchyme and the elongation of the limb. The AER itself is maintained by the **Zone of Polarising Activity (ZPA)** which is found in the posterior base of the limb bud. As a result of inductive influence of the Apical Ectodermal Ridge, the limb starts to elongates and the mesenchymal layer differentiates into cartilage and muscle. Elongation occurs through proliferation of the underlying mesenchyme core, in which the **Apical Ectodermal Ridge** plays a crucial role in ensuring that the mesenchyme immediately underneath it remains undifferentiated.
As growth proceeds, the **proximal mesenchyme** loses signals from the **Apical Ectodermal Ridge** and begins to differentiate into the constituent tissues of the limbs (**cartilages and muscles**). Development of the limb proceeds **proximodistally**. The position of the **AER** is important as it **marks the boundary** between the dorsal and ventral limb ectoderm – AER is able to exert ‘dorsalising and ventralising’ influences over the mesenchyme core. For example, it removes hair follicles from the palms and soles of the feet. **At the 6th week** the distal end of the limb bud becomes flattened forming the **hand and footplates**. These flattened plates are separated from the proximal segments by circular constriction; later on a **second constriction develops** in the limb dividing it into two segments and parts of the limb can be recognised now
Human Limb Development

5 weeks

6 weeks

8 weeks
Fingers and toes are formed by means of cell death in the Apical Ectodermal Ridge, dividing it into five parts.

Growth and development of fingers depend on
1- the five segments of the Apical Ectodermal Ridge,
2- condensation of the mesenchyme to form cartilaginous digital rays,
3- the death of intervening tissue between the rays

Development of upper and lower limbs are similar except that the morphogenesis of the lower limb is 1-2 days behind that of the upper limb.
Development of the hand
Early Forelimb Skeleton

Centres of proliferation precede rarefaction

and subsequent cartilage formation

and advance into the digits

Cell death facilitates separation of the digits

Premuscle masses

1st metacarpal

Trapezium

Scaphoid

Radial nerve

cartilage

perichondrium

condensed mesenchyme

loose mesenchyme

necrosis
During the seventh week of gestation rotation of the limbs takes place.

The upper limb rotates 90° laterally; therefore the thumb lies laterally and the extensor muscles lie on posterior and lateral surface of the limb.

The lower limb rotates 90° medially; thus the big toe lies medially and the extensor muscles are on anterior surface of the limb.
while the external shape of the limb bud is established, mesenchyme in the limb bud starts to condense and differentiates into chondrocytes.

By the sixth week of development, hyaline cartilage models of the bones in the extremities are formed by these chondrocytes.
Endochondral ossification of bones of extremities occurs by the age of 12 weeks. Primary ossification centres are present in all long bones of the limbs by that age. From the primary ossification centre in the shaft (diaphysis), ossification gradually spreads toward the end of the cartilaginous model.

By the time of birth all shaft of bones are ossified except the two ends of the bone (Epiphysis) which remains cartilaginous.

Shortly after birth secondary ossification centres appear in the Epiphyses. Temporally, cartilaginous Epiphyseal plate (metaphysis) remains between the ossification centres in the diaphysis and epiphysis. That plate plays an important role in bone lengthening.
In long bones, epiphyseal plate is present at each end of the bone.

In short bones (phalanges), only one plate is seen.

In irregular bones (vertebrae), many primary and secondary ossification centres are noticed.
Ossification progress when blood vessels invade the centre of cartilaginous model, bringing osteoblasts and restricting proliferating chondrocytes to the epiphyses (ends) of the bone.

Chondrocytes in the diaphysis (shaft) undergo hypertrophy and apoptosis (death), liberating their minerals to the surrounding matrix.

Osteoblasts use these minerals and deposit bone matrix.

Later on as the epiphysis is invaded by blood vessels, secondary ossification centres are formed in the epiphysis.

Bone growth, continues through proliferation of chondrocytes in the epiphyseal plates.
Ossification progress when blood vessels invade the centre of cartilaginous model, bringing osteoblasts and restricting proliferating chondrocytes to the epiphyses (ends) of the bone. Chondrocytes in the diaphysis (shaft) undergo hypertrophy and apoptosis and mineralizes the surrounding matrix. Osteoblasts use these minerals and deposit bone matrix. Later on as the epiphysis is invaded by blood vessels, secondary ossification centres are formed in the epiphysis. The Bone grows, through proliferation of chondrocytes in the epiphyseal plates.
Joint formation

Joints are formed when chondrogenesis is arrested in the cartilaginous condensation and a joint Interzone is established.

Cells in the joint area increase in number and density, followed by the formation of joint cavity through cell death.

The surrounding cells then differentiate into capsule of the joint.
Joint formation

- Interzone condensation
- Joint specification
- Secondary structure induction and cavitation
- Joint maturation

**Diagram Key:**

- Col2a1
- Interzone
- Col2a1^NeqGdf5^High
- Col2a1^Lo-Gdf5^High
- Proliferative chondrocyte
- Prehypertrophic chondrocyte
- Hypertrophic chondrocyte
- Meniscal progenitor
- Ligament progenitor
- Synovial progenitor
- Articular progenitor
- Bone
- Meniscus
- Ligaments
- Synovium
- Articular cartilage

**e** Joint homeostasis

- Femur
- Patella
- Articular cartilage
- Meniscus
- Ligament

**f** Joint degeneration

- Normal joint space
- Bone spurs
- Cartilage loss
- Joint space narrowing
Limb Innervation
Ventral rami of the spinal nerves invade the limb bud mesenchyme and contribute in its innervation

The upper limb is supplied from 5th - 8th cervical and first thoracic spinal segments (brachial plexus)

The lower limb is supplied from the 2nd - 5th lumbar and first 3 sacral spinal segments (lumbosacral plexus)

• Plexus forms as nerves invade the limb bud mesenchyme

• Fetal period - touch pads (tactile sensation) become visible on hands and feet.
Clinical Relevance – Limb Abnormalities

Congenital limb and digit defects occur in between 1 in 500 and 1 in 1000 live births. They are often associated with other birth defects, such as congenital heart malformations.

The common limb abnormalities are:
**Amelia** – complete absence of a limb.
**Meromelia** – partial absence of one or more limb structures.

The common digit abnormalities are:
**Syndactyly** – fusion of digits, which occurs due to a lack of apoptosis between the digits during development.
**Polydactyly** – increased number of digits
Thank You