# Organogenesis

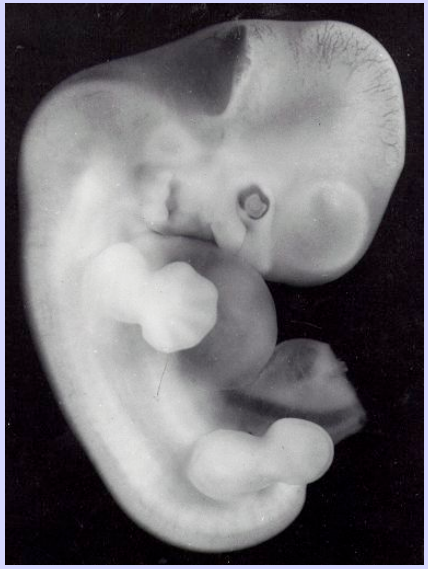
After the completion of gastrulation the embryo enters into organogenesis – this is the process by which the ectoderm, mesoderm and endoderm are converted into the internal organs of the body.

This process takes place between about week 3 to the end of week 8. At the end of this period the embryo is referred to as a fetus.

The development of the limbs is a good example of the types of processes that are involved in organogenesis.

4 weeks ~ 5mm

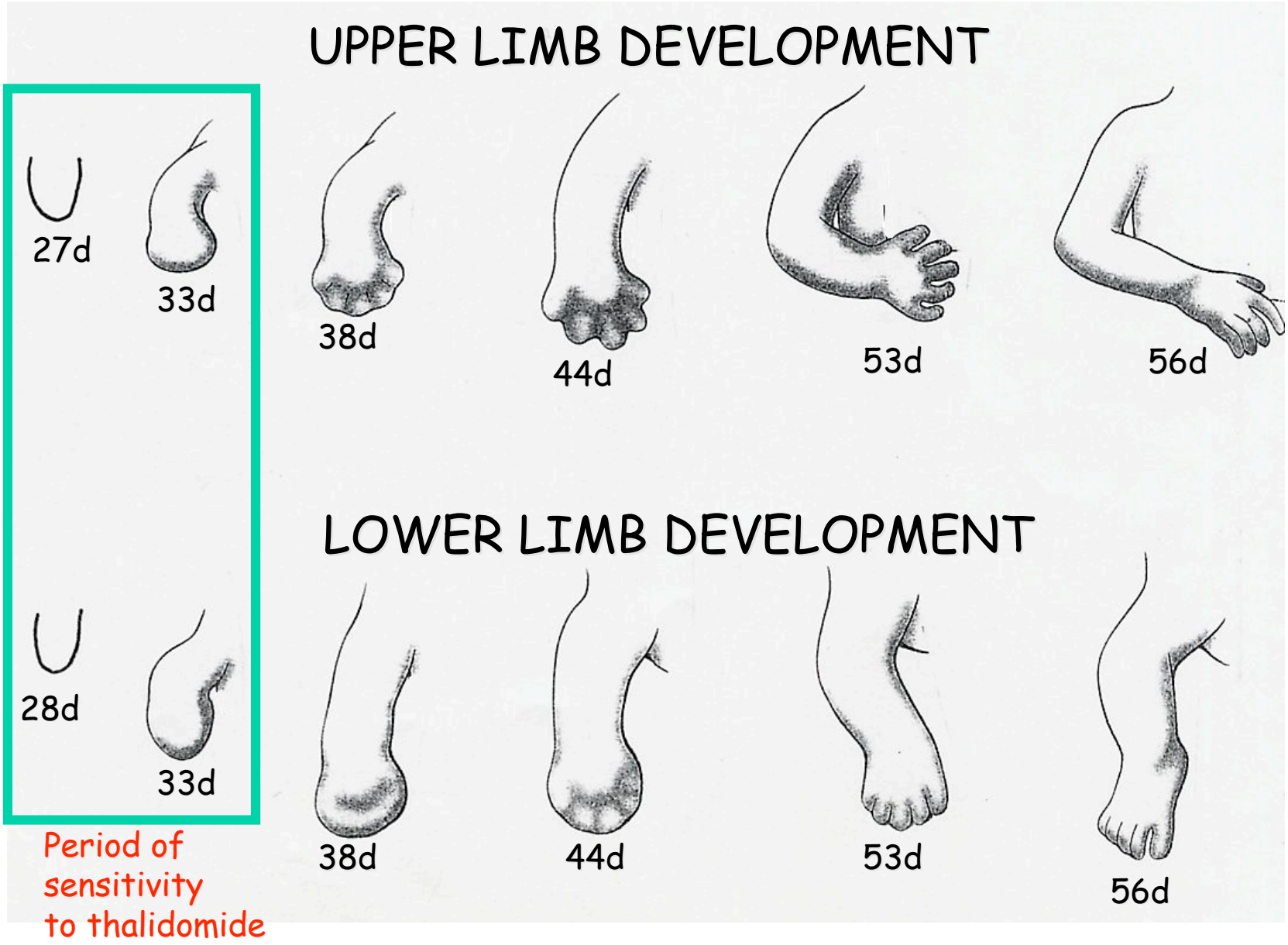
5 weeks ~ 10 mm



6 weeks ~ 13 mm

8 weeks ~ 3 cm

Images are from the Human Developmental Anatomy Centre, National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington DC20306



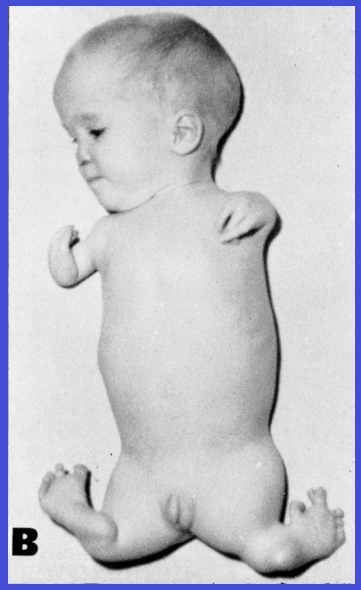

Adapted from Fig 11.3 Essentials of Human Embryology by William Larsen 1998 Churchill Livingstone

# THALIDOMIDE

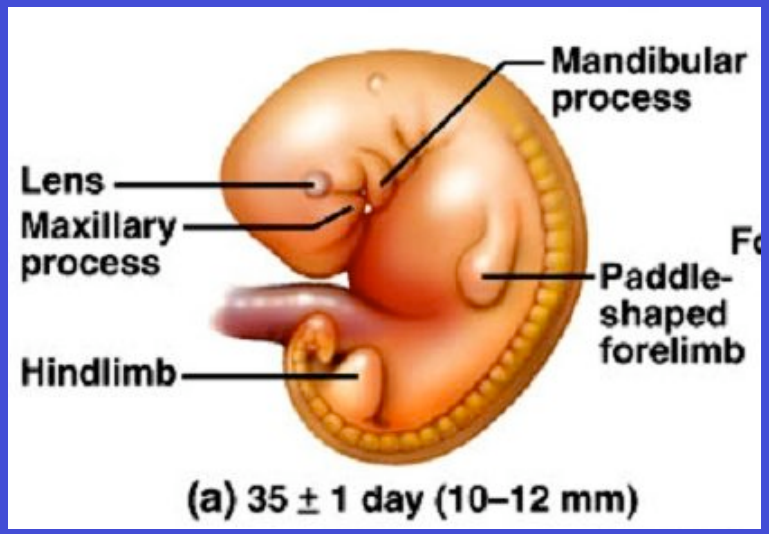
Marketed 1957-1961 initially as a sedative and sleeping tablet and subsequently used to treat nausea and vomiting in pregnancy.

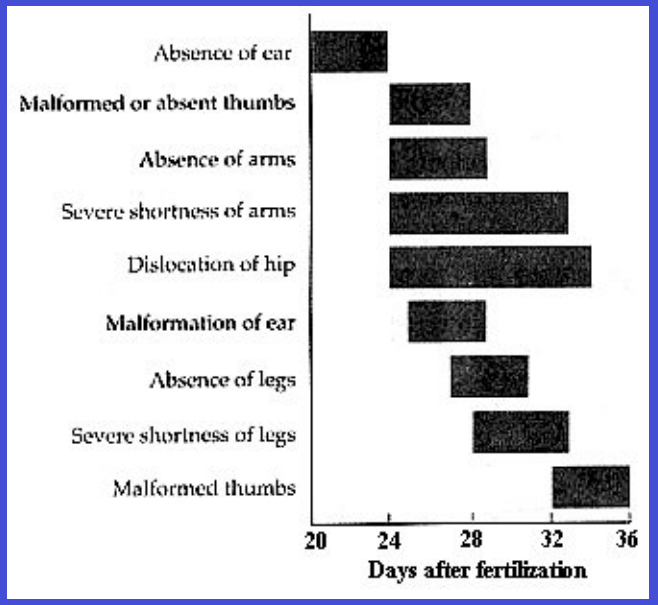
Used in Australia, Germany, Japan, Britain, Brazil, Sweden and Italy.

Exposure to the drug in early pregnancy resulted in severe malformations in nearly 10,000 children.




Courtesy Dr. M Edgerton,
Dept Plastic Surgery
University of Virginia
In: Langman's Medical
Embryology Sadler, 1985
Copyright Williams and Wilkins




Sensitive times for induction of thalidomide defects

www.clt.astate.edu/mgilmore/A&P%202/Pregnancy,%20Growth%20and%20Development.ppt

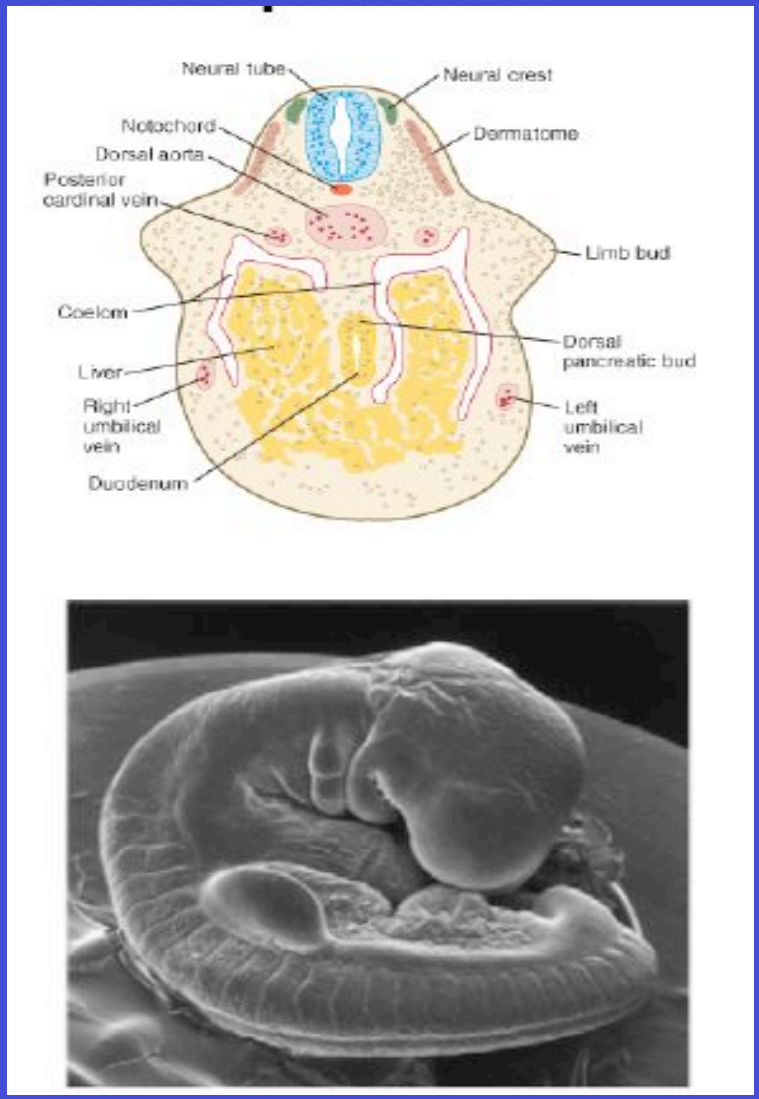
# Limb Development

Limb development begins with the activation of the lateral mesoderm which begins to produce FGF10.

FGF10 knockout mice are limbless.

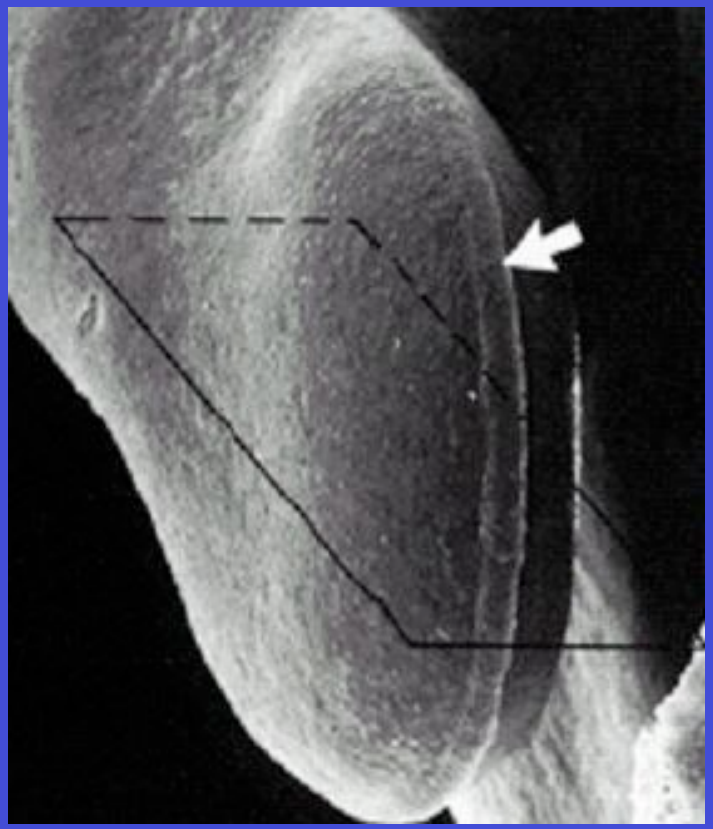

The newly formed limb bud consists of a layer of ectoderm overlying a core of mesoderm.

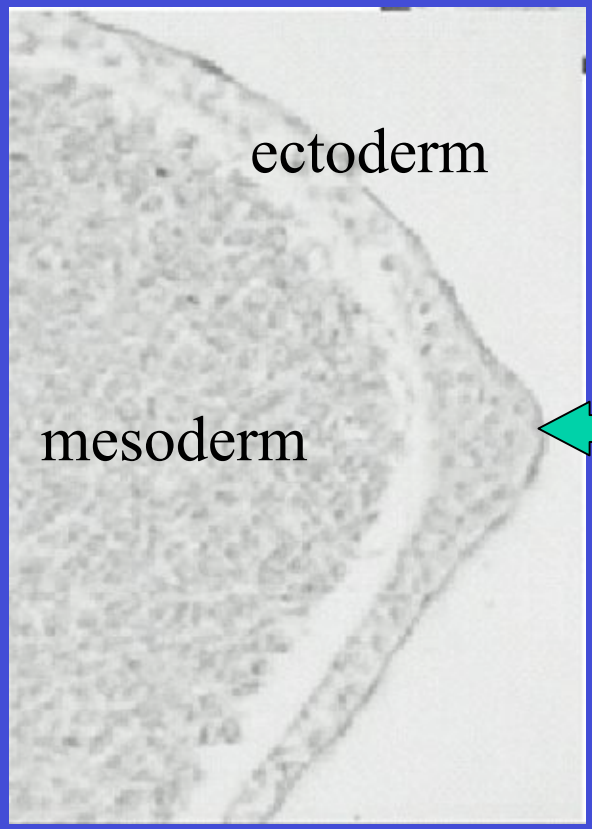
SEM photomicrograph of a 4-week human embryo ~ 4 mm in length




136.165.37.172/PDF/348lecture24.pdf -

# EARLY LIMB BUD AND THE APICAL ECTODERMAL RIDGE






From Essentials of Human Embryology W. Larsen Churchill Livingstone 1998

The cells of the AER produce fibroblast growth factor (FGF-8) and later FGF-2 and FGF-4) which diffuse about 200 micrometres into the mesoderm. They cause the adjacent zone of mesodermal cells to keep dividing and stops them from differentiating.

# THE POSITIONAL THEORY OF LIMB DEVELOPMENT

Over a short period lasting from about day 26 to day 33 all the cells in the limb bud become "determined" to form a particular part of the adult limb.

This determination occurs by the development of 3 axes in the limb bud.

(i) Proximodistal – signal comes from the apical ectodermal ridge and involves FGF-8

(ii) Anteroposterior – signal comes from zone of polarising activity - ZPA and involves sonic hedgehog

(iii) Dorsoventral – signal from dorsal ectoderm – Wnt-7a and a signal from the ventral ectoderm En-1.

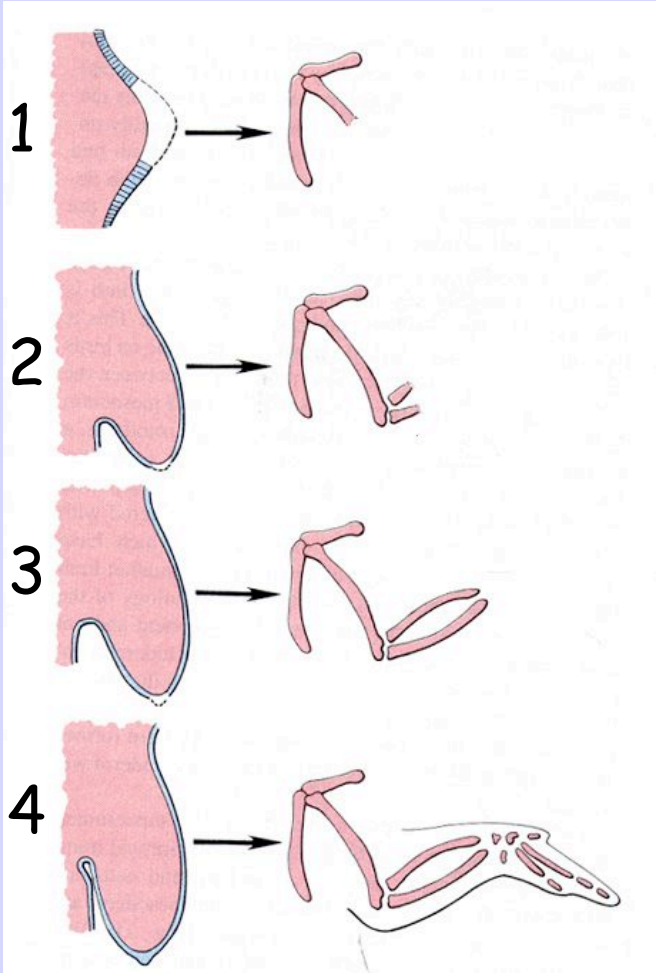
# Proximal-distal axis

# Role of the AER in proximodistal differentiation

The cells of the AER produce fibroblast growth factor (FGF-8) and later FGF-2 and FGF-4) which diffuse about 200 micrometres into the mesoderm. They cause the adjacent zone of mesodermal cells to keep dividing and stops them from differentiating.

Experiments with the chick limb bud show the effects of removing the AER at successively later stages of development. 1 = 3 days, 2 = 3.5 days, 3 = 4 days.

The more mature the limb bud at the time of AER removal the more skeletal elements form.

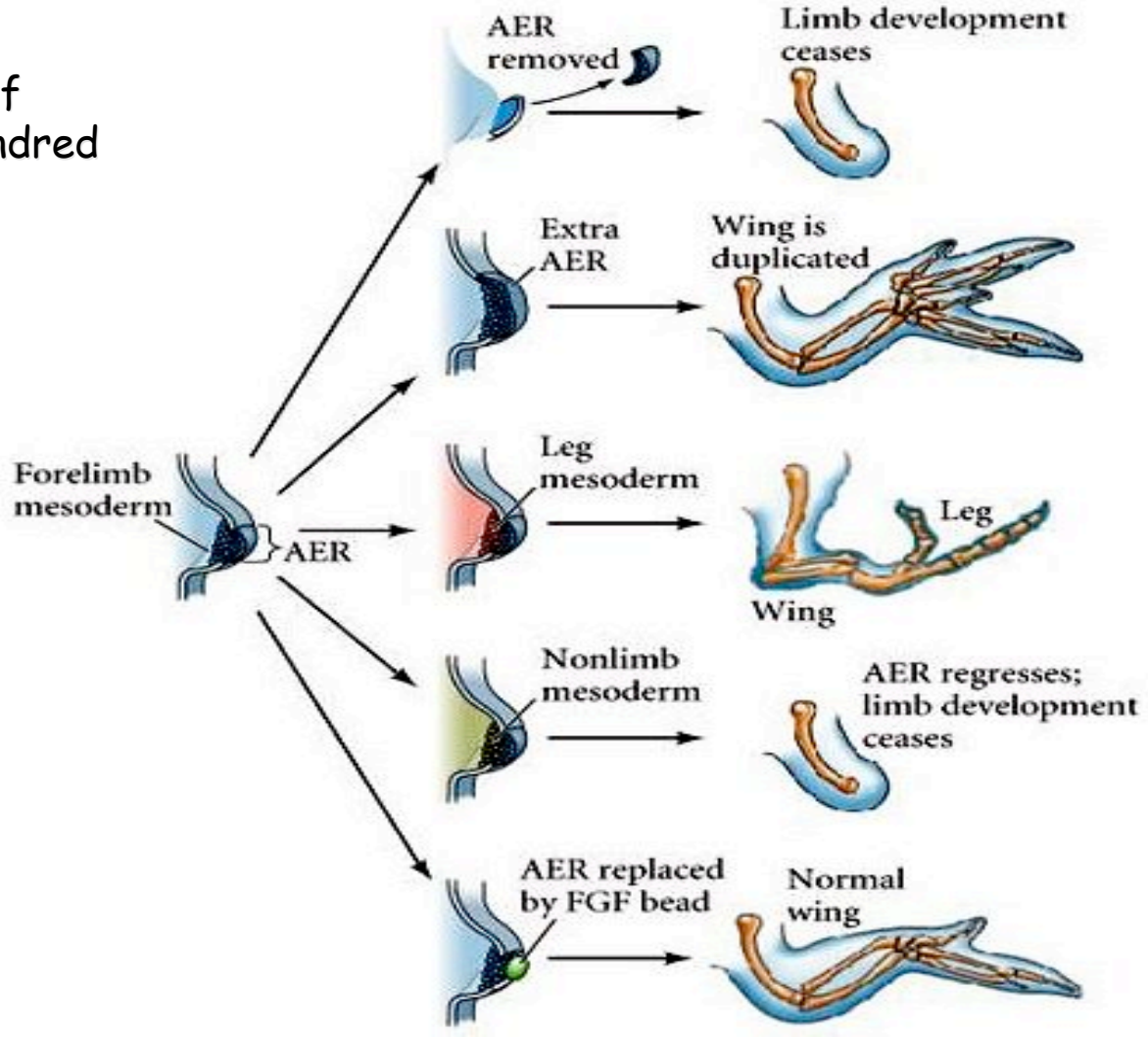



Saunders JW J Exp Zool 108:363-403 (1948)

Fig 10-7 Human Embryology and Developmental Biology by BM by Carlson, Mosby Inc 2004

# Role of the Apical Ectodermal Ridge

It produces different types of FGF which diffuse several hundred micrometres into the underlying mesoderm.




courses.biology.utah.edu/.../Lec13Limb.html

# Anterior-posterior axis

# ZONE OF POLARISING ACTIVITY AND THE ANTEROPOSTERIOR AXIS

At the posterior margin of the limb bud there is a small group of cells known as the zone of polarising activity (ZPA). These cells produce the protein sonic hedgehog which sets up a gradient across the limb bud.

Sonic hedgehog in the ZPA

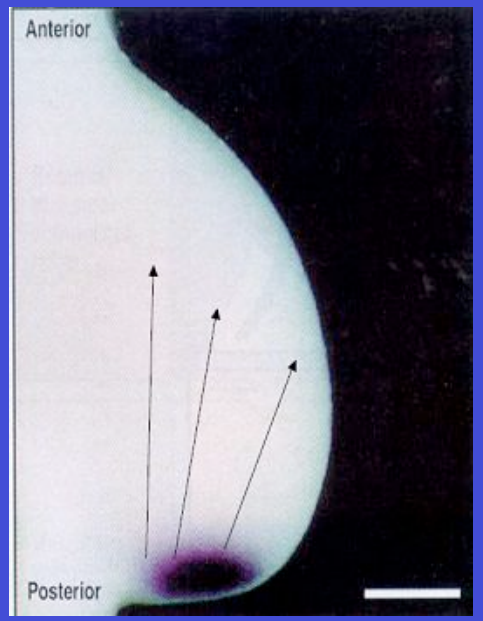
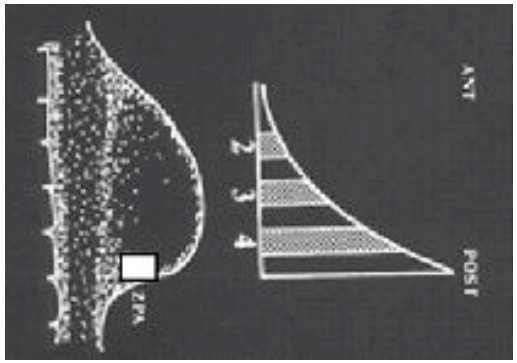
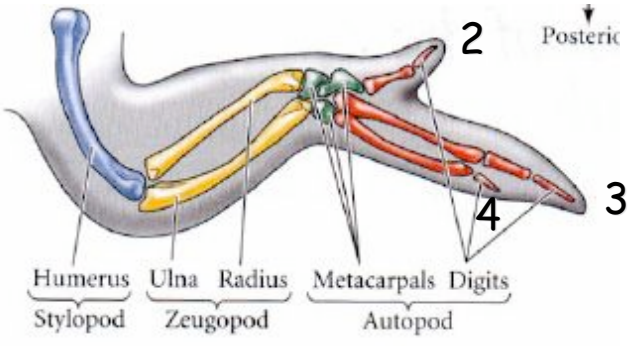



Image adapted from Principles of Developmental, Ed. L. Wolpert, Oxford Univ. Press, 1998)

# ZPA and the anteroposterior axis

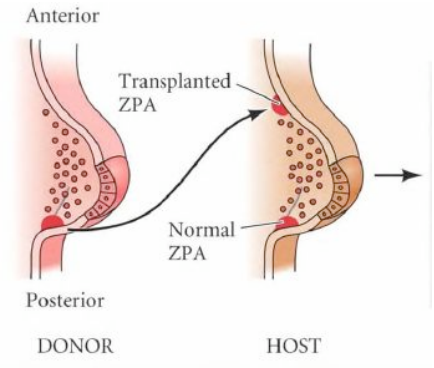
A

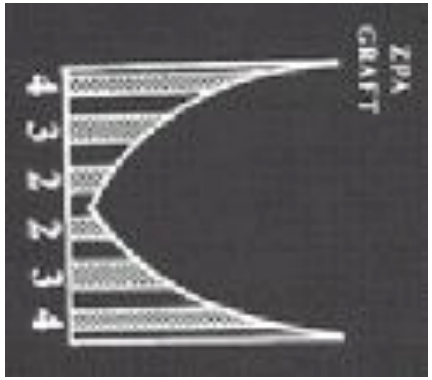


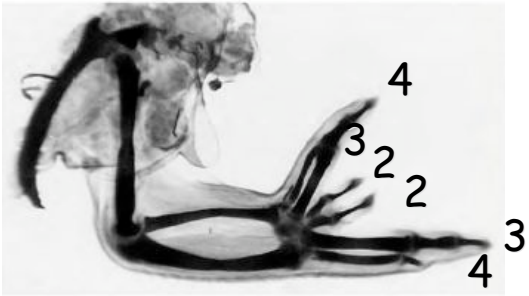




In the normal chick limb bud the ZPA establishes a gradient across the limb and this determines digit formation

B



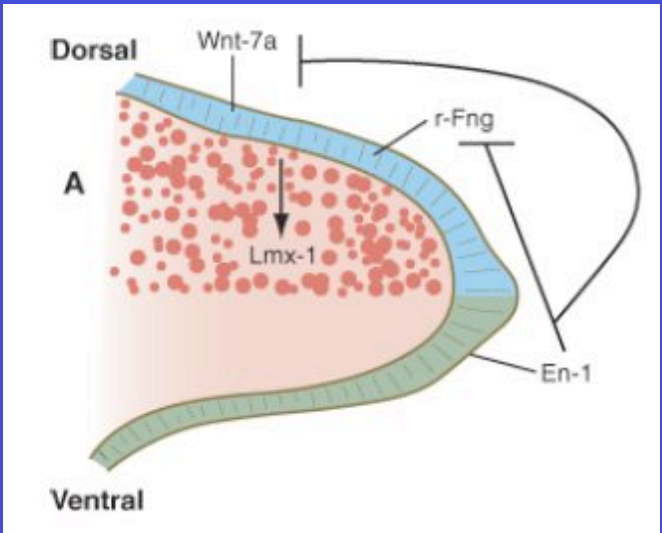

If a second ZPA is transplanted into the anterior end of the limb bud it causes a mirror image gradient and mirror image digital development

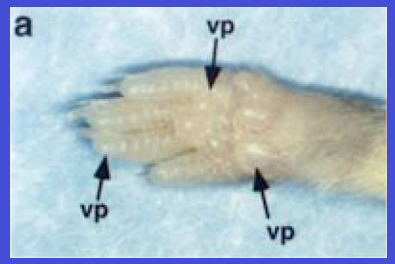
# Dorsal-ventral axis

# Dorsoventral differention is controlled by the surface ectoderm

The AER separates the dorsal ectoderm from the ventral ectoderm. Differentiation of the dorsal surface is controlled by Wnt-7a – a secreted gene product of the dorsal ectoderm. Wnt-7a knockout mice display dorsal to ventral transformation of the limbs.

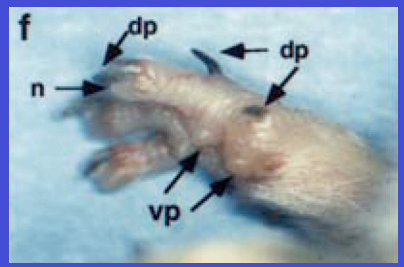
The ventral ectoderm expresses Engrailed-1 (En-1) – a transcription regulator. En-1 knockout mice show ventral to dorsal transformation.




normal ventral


normal dorsal




dorsal surface Wnt-7 knockout

Fig 10-14 Human Embryology and Developmental Biology by BM Carlson, Mosby Inc 2004

http://www.colorado.edu/MCDB/MCDB4650_Fall/17ppt.pdf#search=%22Wnt-7a%20knockout%20%22

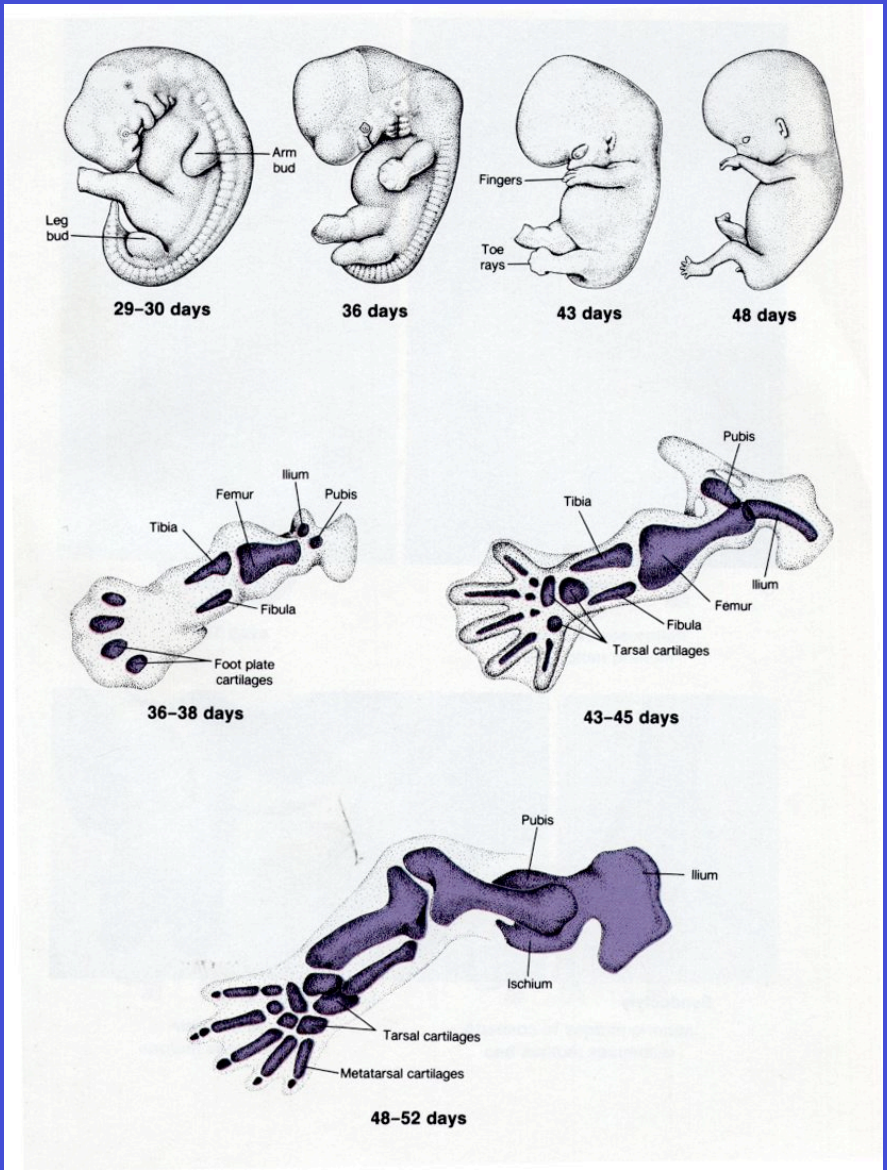
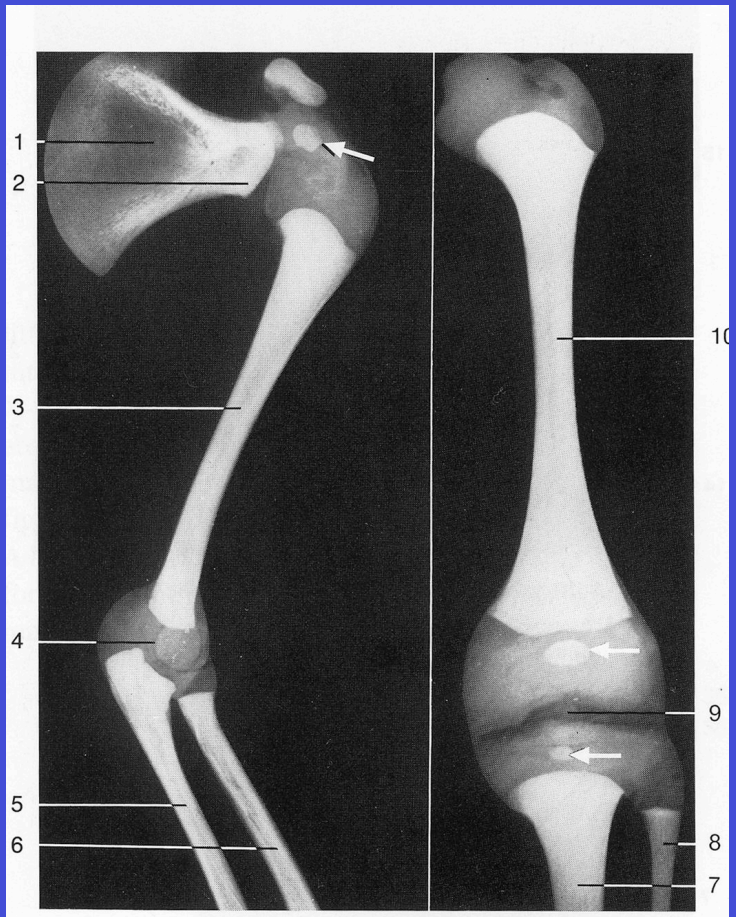



Diagram shows the cartilaginous precursors of the bones.

Migratory cells must still enter the limb bud to supply:

Muscles
Nerves
Blood vessels

From Langman's Medical Embryology, TW Sadler, 1985 Williams and Wilkins




**X-ray of the upper and lower limb of a newborn child.**
Left: upper limb. Right: lower limb.
Arrows: ossification centers.

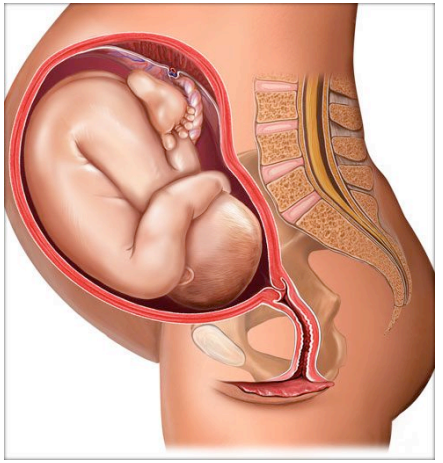
| | | | | | |
|---|---|---|---|---|---|
| 1 | Scapula | 4 | Elbow joint | 7 | Tibia |
| 2 | Shoulder joint | 5 | Ulna | 8 | Fibula |
| 3 | Humerus | 6 | Radius | 9 | Knee joint |
| | | | | 10 | Femur |

Image from Colour Atlas of Anatomy
JW Rohen et al., 2002
Lippincott Williams & Wilkins

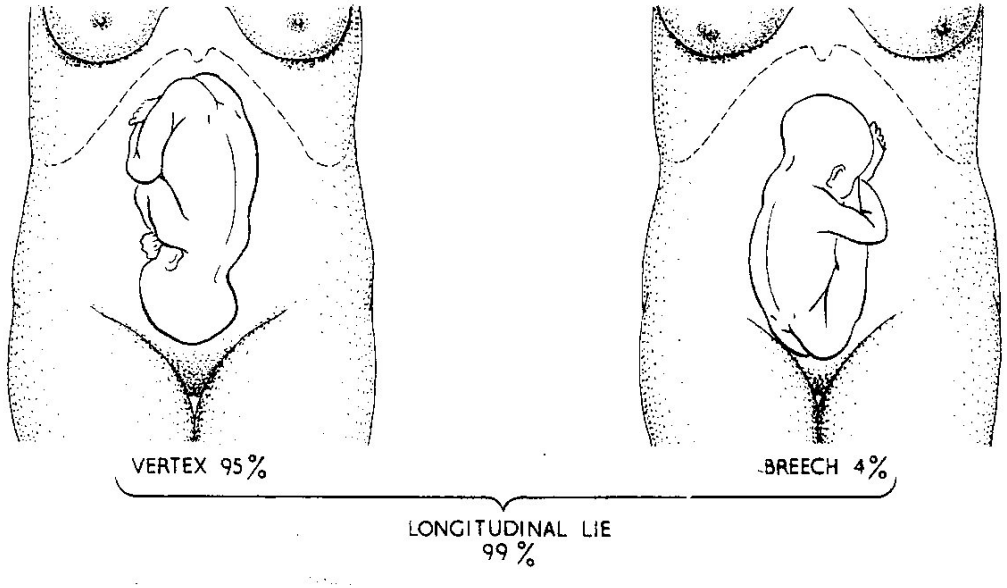
# Fetal movement

10 weeks – 6cm

16 weeks – 14 cm



38 weeks – 36 cm



# Congenital Hip Dysplasia

Congenital hip dysplasia a condition in which the hip joint is unstable and easily dislocated at birth. The hip joint is usually stablised by the surrounding ligaments but these are loose and stretched in this condition.

It has been estimated that 1 in 100 newborn infants have clinically unstable hips but only 1 in 1,000 experience a true dislocation.

There is a 9:1 female predominance; apparently the baby's own female hormones must aggravate the abnormal looseness of the hip ligaments.

Of children with DDH, approximately 60% are firstborn

30-50% develop in the **breech position;** 2% to 4% of all babies are breech presentations, but about 20% of DDH patients are born breech.

The prevalence of DDH in females born in breech position is as high as 1 case in 15 persons.

***Figure 3A –*** *Pre-operative.*

***Figure 5A –*** *Late post-operative.*

FINISH!