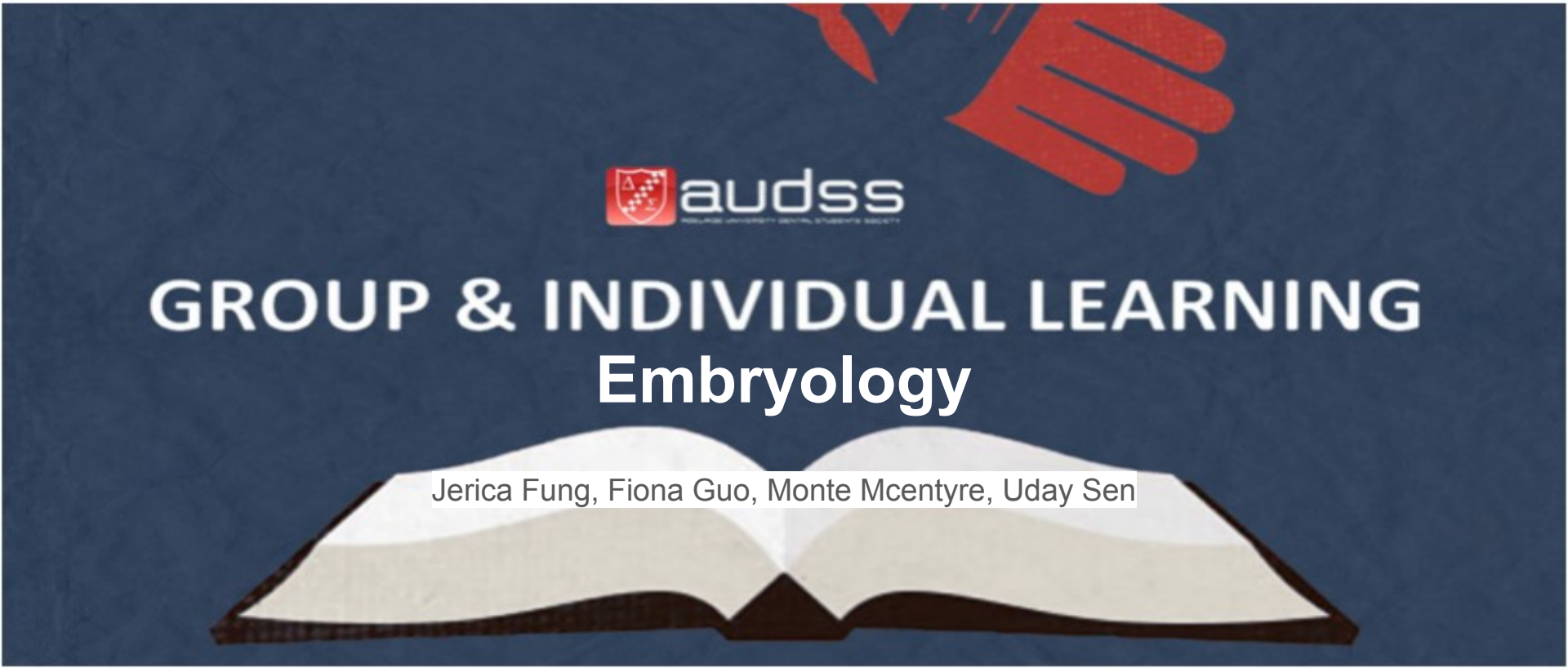
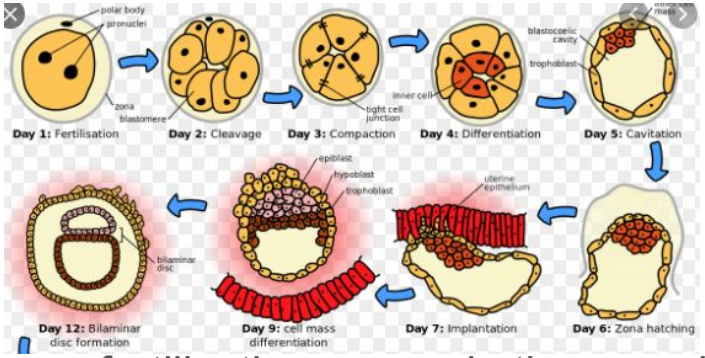


Embryology

Jerica Fung, Fiona Guo, Monte Mcentyre, Uday Sen

Week 1 Proliferative phase



Day 0 → Fusion of male and female gametes → fertilisation occurs in the ampulla → Zygote

Day 1 -2 → Blastomere → 2 cells → rapid division within the confined space

Day 3 → Morula → solid sphere of cells → division that occurs from male/ female gametes fusion

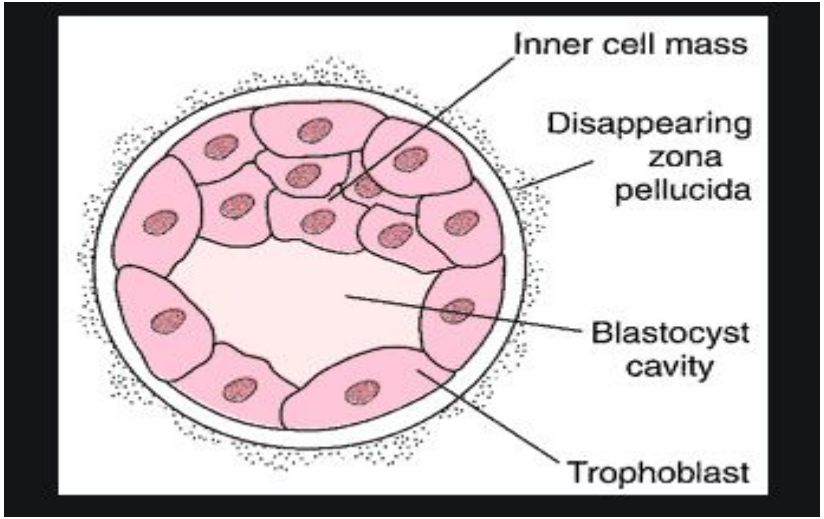
Day 5-6 → Blastocyst → Outer cell mass (Trophoblast), Inner cell mass and Blastocyst cavity

Day 7 → Implantation of the Blastocyst into the uterine epithelium → Invasion of the trophoblasts into the uterus.

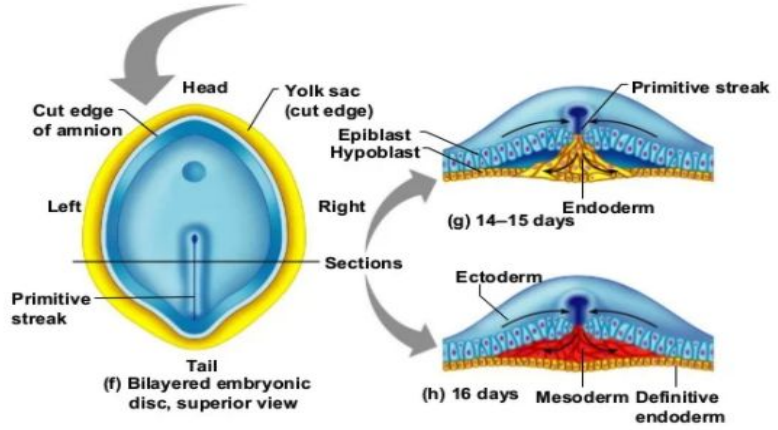
Week 2

Day 9 → Blastocyst now inside the uterus → Trophoblasts differentiate allow for continued development from the embryo ie hcG production.

Also Embryoblast differentiate into **epiblast** and **hypoblast,** there is also formation of the amniotic cavity and yolk sac



Week 2 **Gastrulation**



Primitive streak develops in the Epiblast layer.

Cells then move from the primitive streak into the layer between the epiblast and hypoblast.

These epiblast cells will then transform into the three germ layers

Ectoderm, Mesoderm and Endoderm

The hypoblast cells will be displaced (never part of the embryo ie just yolk sac)

Week 4 (Neurulation)

1. Neural Tube formation
2. Formation of the branchial arches
3. Formation of the tongue

Week 4 Neurulation → Histodifferentiation and division

3 Germ layers begin to fold in 2 different dimension rostrocaudally (important for oral cavity) and laterally (puts ectoderm on outside)

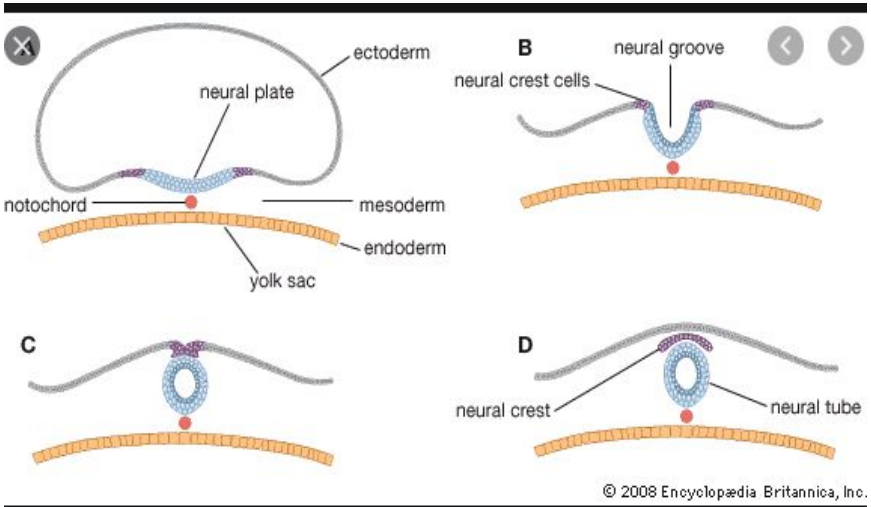
Causes the Neural fold → Neural tube with Neural crest cells on top→ Neural tube will become brain and spinal cord → Neural crest cells peripheral nervous system.

Mesoderm has three main components → Paraxial (somite ie muscles), Intermediate (Gonads and Kidneys), Lateral plates (Somatic and Splanchnic ie Heart circulatory)

Endoderm → GI system

Ectoderm → Skin ie epidermis

Notochord is the support for the embryo



Ectoderm	Mesoderm	Endoderm
Epidermis - Nails - Hair - Sebaceous glands - **Enamel** - Paraxial Mesoderm - Brain - Spinal Chord - PNS - Motor neurons	- Muscle (both skeletal and smooth) - Skeleton - Cartilage - CT - Adipose tissue - Circulatory and Lymphatic system - Pericardium - Dermis - Urinary tract - Notochord	Epithelial lining of GI tract (except mouth, see ectoderm) - Epithelial lining of glands of the GI tract - Organs - Stomach - Colon - Liver - Bladder - Trachea - Lungs - Thyroid and Parathyroid - Intestines

Formation of branchial arches

Forebrain	First bulge
Midbrain	Second bulge
Hindbrain	Next 8 bulges → Termed Rhombomeres

Midbrain, Forebrain and Hindbrain are formed during folding

Branchial arch 1 (integral to facial development) → arises from the **Midbrain** and **Rhombomere 1 and 2**

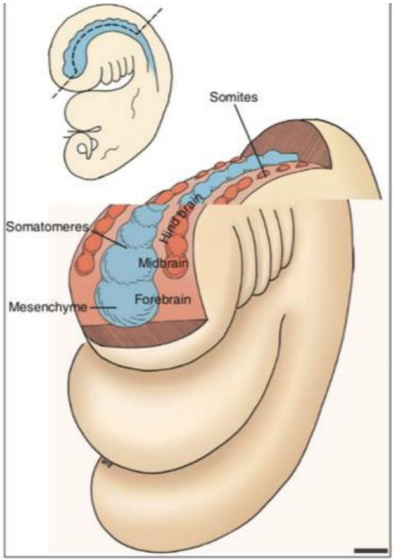
Branchial arch 2 → arises from **Rhombomere 4**

This point of development is highly dependent on correct temporal

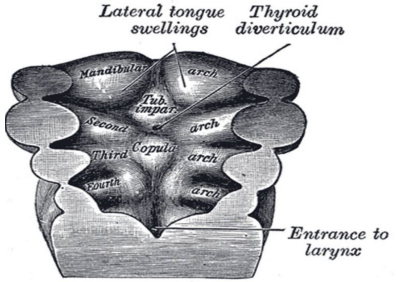
Expression of transcription factors. For appropriate NCC migration.

Rhombomere 6 → arch 3

Rhombomere 8 → arch 4



Tongue development Weeks 4-7



Formed by pharyngeal arches 1, 2, and 3

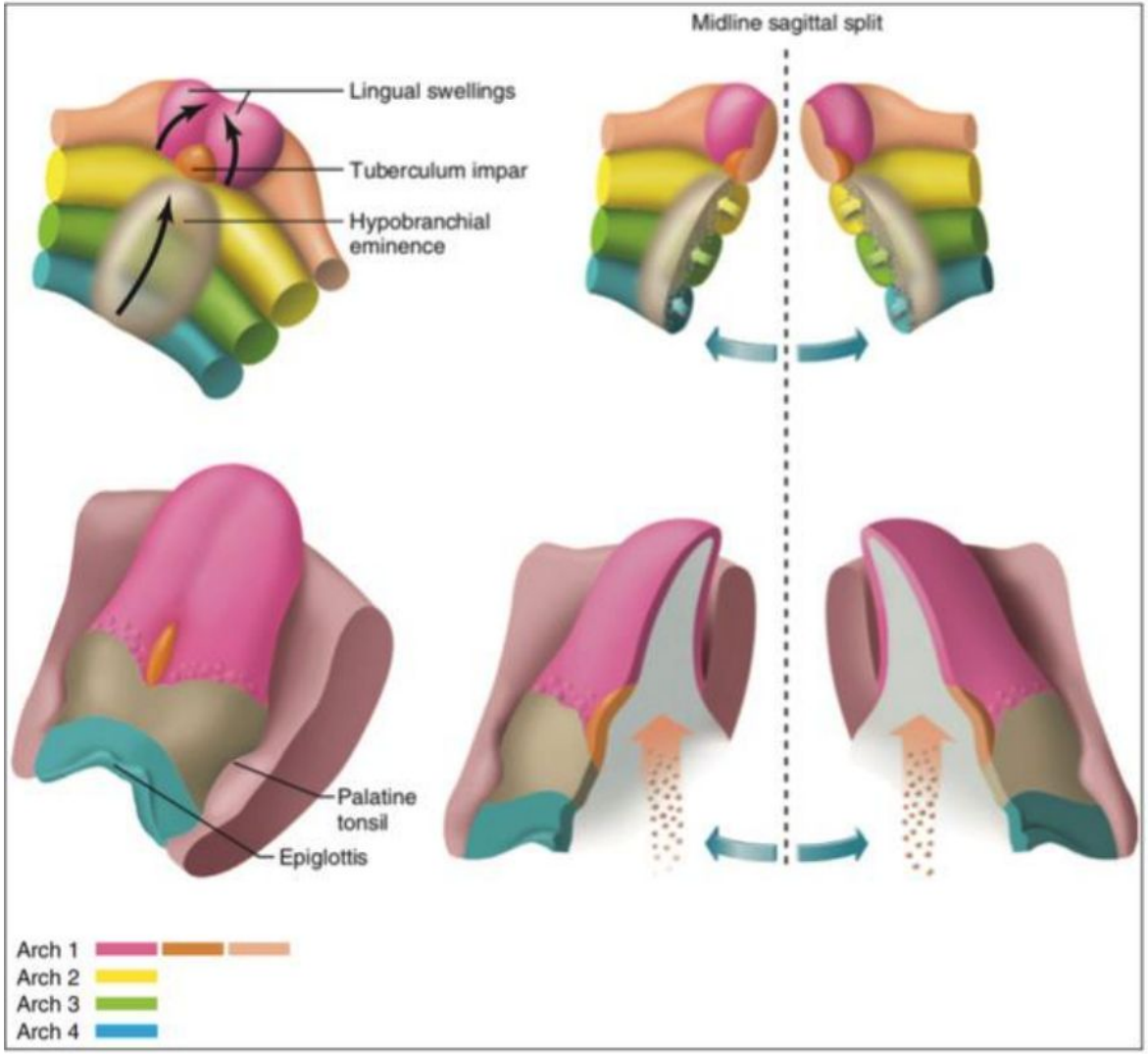
Anterior ⅔ of the tongue formed by two lateral swellings and the tuberculum Impar converging.

Root of the tongue → formed by the copula (2nd arch) and hypobranchial eminence (arch 3 and 4).

Copula is overgrown

Most posterior part of the 4th arch mark the epiglottis.

Muscles of the tongue arise from the occipital somites → migrate forward → supplied by CN 12


Midline sagittal split
Lingual swellings
Tuberculum impar
Hypobranchial eminence
Palatine tonsil
Epiglottis
Arch 1
Arch 2
Arch 3
Arch 4

Week 5 Facial Development.

formation and fusion of several processes and prominences

OLFACTORY PLACODE & NASAL PROCESS DEVELOPMENT (day 28)

- Localised thickening develops within the ectoderm of the frontal prominence, above opening of the stomatodeum
- Rapid proliferation of underlying mesenchyme bulges the frontal eminence forward → horseshoe shape ridge
- Converts the olfactory placodes into the nasal pit
- Lateral arm of horse shoe → lateral nasal process
- Medial arm of horse shoe → medial nasal process

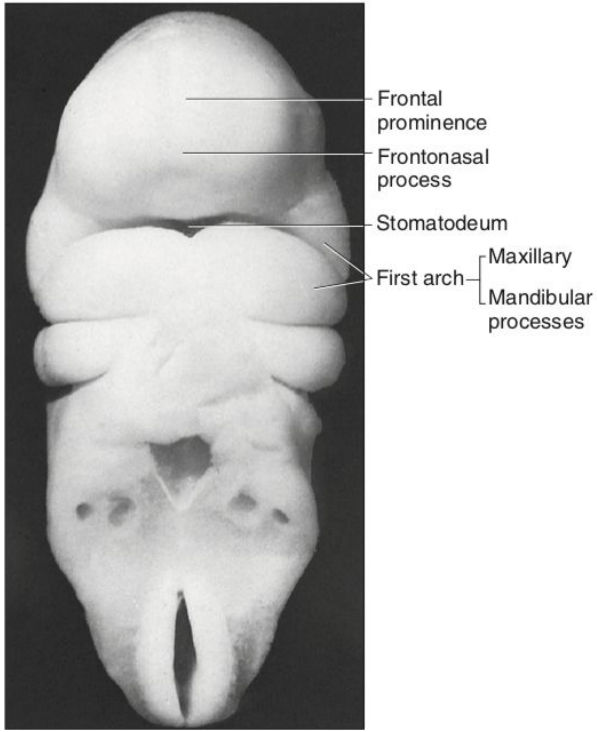


FIGURE 3-12 A 27-day-old embryo viewed from the front. The beginning elements for facial development and the boundaries of the stomatodeum are apparent. The first arch gives rise to maxillary and mandibular processes. (Courtesy of H. Nishimura.)

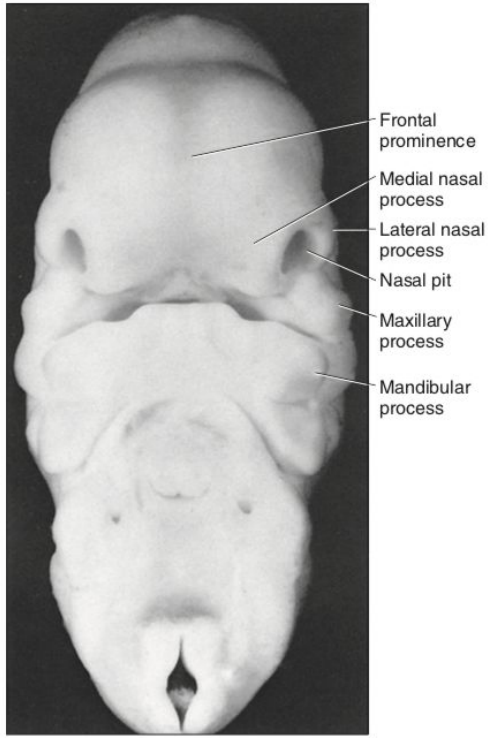


FIGURE 3-13 A 34-day-old embryo viewed from the front. The nasal pits have formed, thereby delineating the lateral and medial nasal processes. (Courtesy of H. Nishimura.)

Week 6:
Formation of upper lip & philtrum, anterior maxilla & primary palate

- Maxillary process grows medially and approaches the lateral and medial nasal process
- Nasolacrimal groove & bucconasal groove separates them
- Medial nasal processes displaced to the midline and merges, forming the upper lip & philtrum, anterior maxilla & primary palate

Formation of the lower lip

- Merging of the 2 streams of ectomesenchyme of the mandibular process at the midline

Formation of nasolacrimal duct

- Merging of lateral nasal process & maxillary process (previously separated by the nasolacrimal groove)
- Epithelium in the floor of the groove forms a solid core that separates from the surface and forms a canal → nasolacrimal duct
- After the duct has separated, the 2 lateral nasal processes merge by infilling of mesenchyme


Lateral nasal process
Medial nasal process
Groove separating the maxillary process from the lateral nasal process (naso-optic groove)
Maxillary process
Groove separating the maxillary process from the medial nasal process (bucconasal groove)

Processes merging	Groove separating the processes	The future of the processes
Left and right medial nasal processes	NA (no name)	- Philtrum - Part of the maxilla carrying incisors **- Primary palate**
Medial nasal process Maxillary process	Bucconasal groove	- Lateral aspect of upper lip
Lateral nasal process Maxillary process	Naso-optic groove (naso-lacrimal groove)	- Nasolacrimal duct (forms beneath naso-optic groove)

Week 6: formation of the rudimentary mandible

- Meckel’s cartilage (hyaline cartilage) forms the lower jaw in the primitive vertebrates
- Extends from the developing ear region to the midline of the fused mandibular process
- Mandibular branch of the trigeminal nerve begins ⅔ along the length of the cartilage which divides into the lingual and inferior alveolar branches

Week 7: formation of the body of the mandible

- Intramembranous ossification begins
- Occurs at the splitting of the IAN into the incisal and mental branch
- Bone formation spreads rapidly to the midline and posteriorly towards the point where the Md nerve splits into the lingual and IAN
- Two areas of ossification remains separate until mandibular symphysis occurs shortly after birth

Week 7: formation of the ramus of the mandible

- The ramus of the mandible develops by rapid spread of ossification posteriorly into the mesenchyme of the first arch, turning away from the meckel’s cartilage
- The “turn away” of ossification from the meckel’s cartilage is marked by the lingula
- At 10 weeks, rudimentary mandible is formed

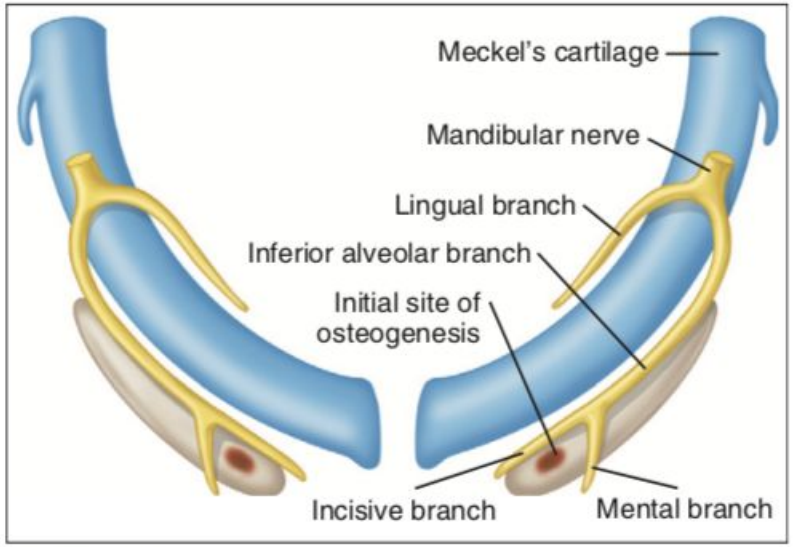


FIGURE 3-27 Site of initial osteogenesis related to mandible formation. Bone formation extends from this anteriorly and posteriorly along Meckel's cartilage.

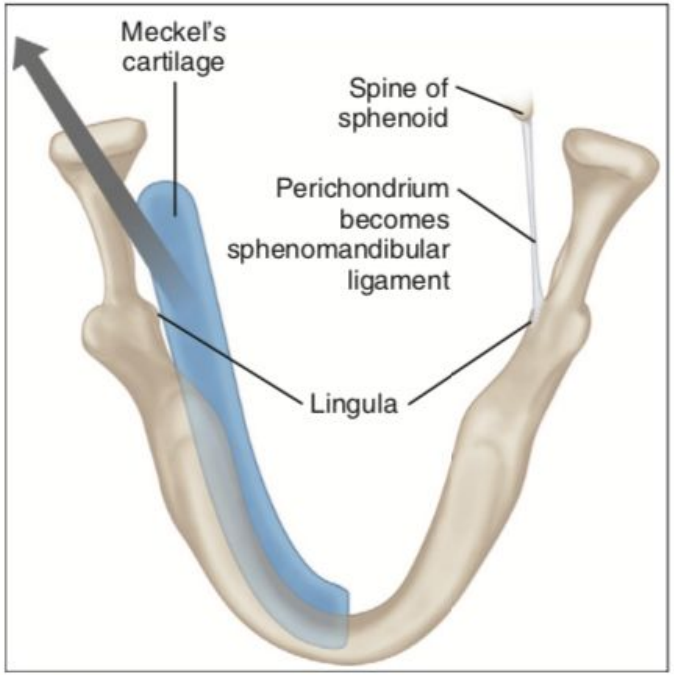


FIGURE 3-29 Spread of mandibular ossification away from Meckel's cartilage at the lingula.

Formation of the maxilla

- Centre of ossification appears in the angle between the anterosuperior dental nerve which is given off from the inferior orbital nerve
- Bone formation spreads posteriorly below the orbit towards the zygoma and anteriorly towards the incisor region

Week 7-8: formation of secondary palate

- Nasal septum grows downwards front the frontonasal process along the midline
- 2 palatine shelves/processes extends from the maxillary process towards the midline
- Palatine shelves grow/directed downwards on each side of the tongue
- At week 8, Tongue is withdrawn between shelves → shelves proceeds to elevate and fuse with each other + primary palate + nasal septum
- Separation of the primitive oral cavity into Nasal and Oral cavity
- Closure of the secondary palate proceeds gradually from the primary palate in a posterior direction

Week 9: fusion of the palatine shelves

- Requires elimination of the epithelial covering of the shelves
- As the 2 shelves meet and fuse, adhesion of epithelium occurs and a midline epithelial seam consisting of 2 layers of basal epithelial cells form
- Epithelial seam thin and broken down to permit ectomesenchymal continuity → breaking up to form discrete islands of epithelial cells
- Epithelial cells loses their epithelial characteristic assuming fibroblast-like features, differentiating into mesenchymal cells

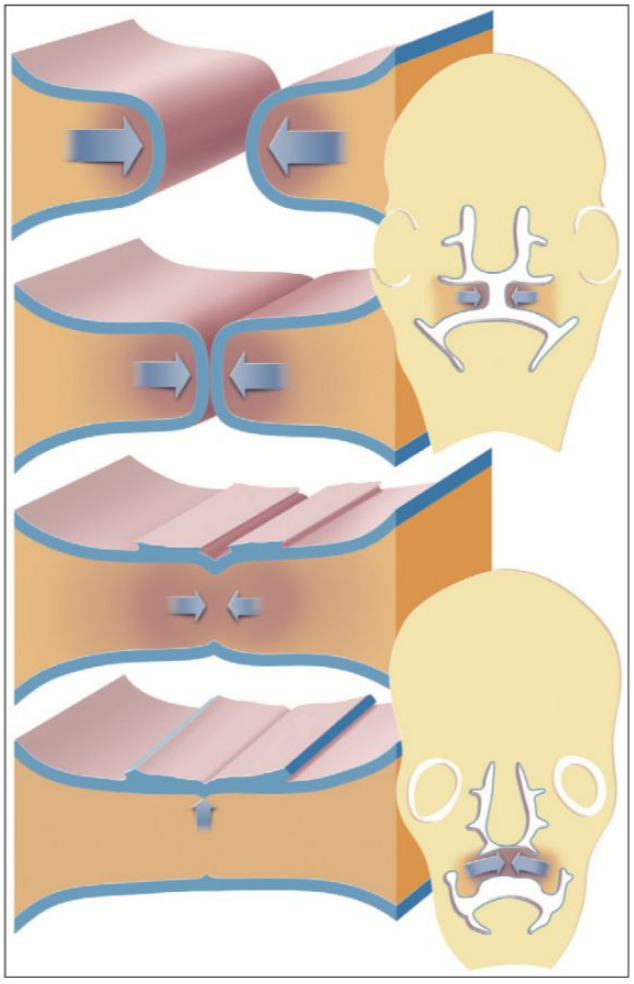


FIGURE 3-11 During palate formation, there is fusion of palatal processes, involving the breakdown of surface epithelium.

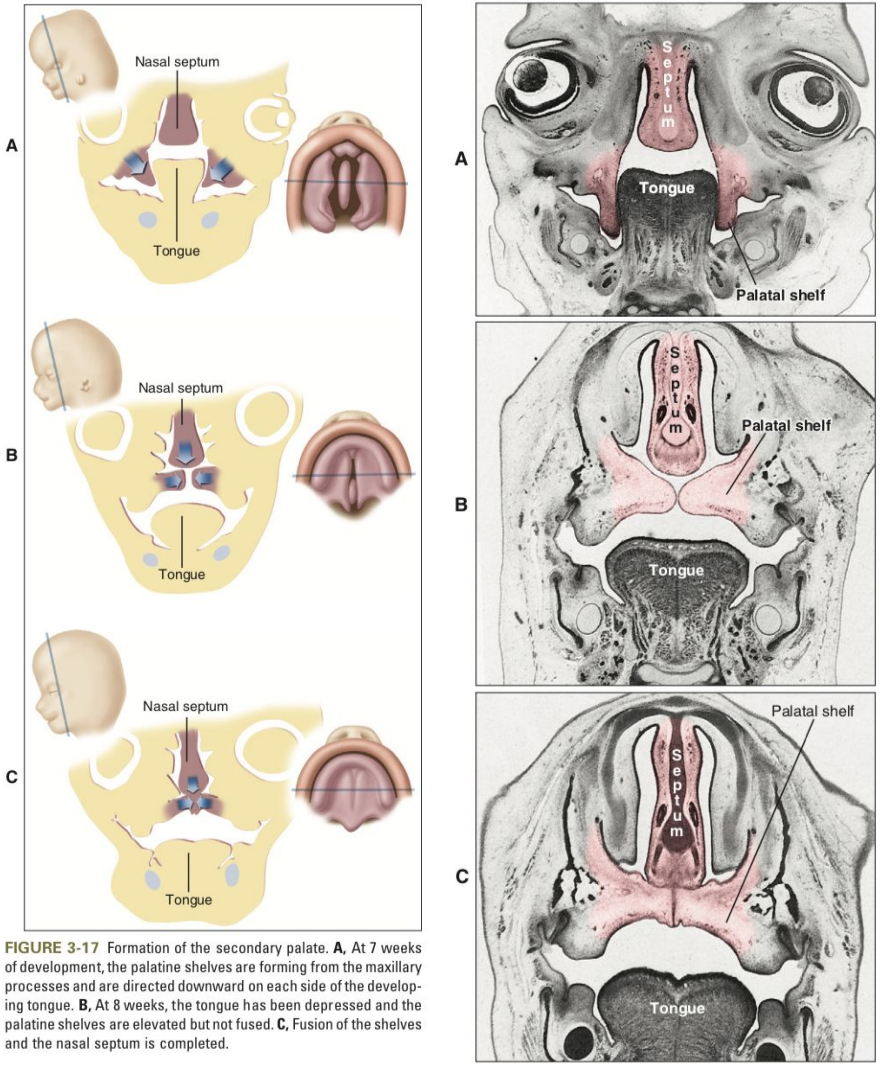


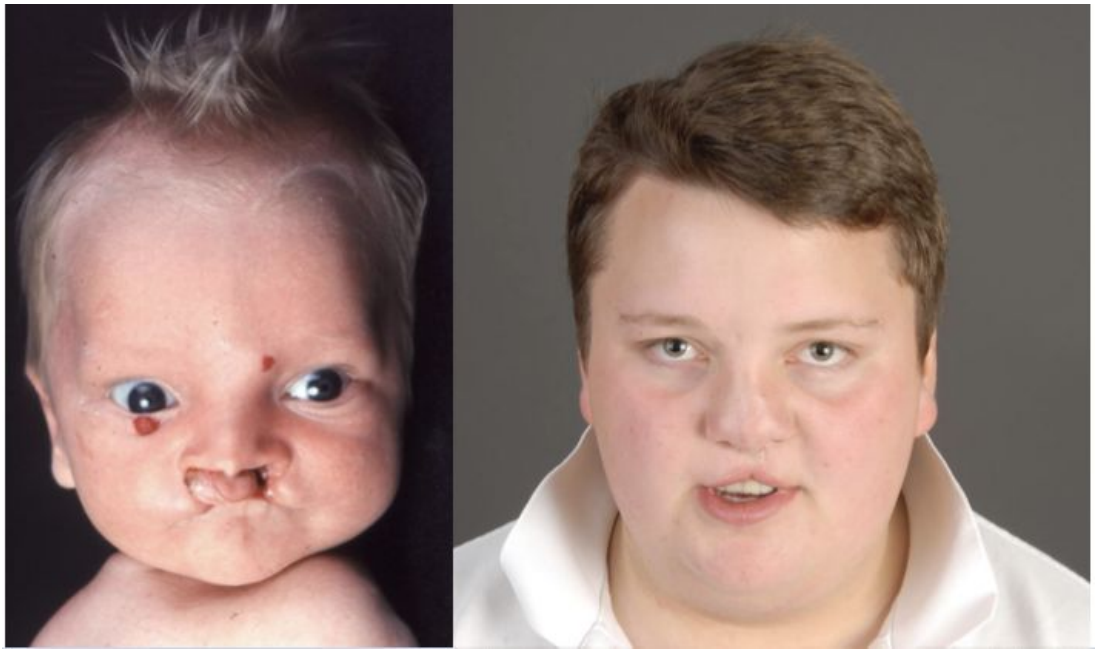
FIGURE 3-17 Formation of the secondary palate. **A,** At 7 weeks of development, the palatine shelves are forming from the maxillary processes and are directed downward on each side of the developing tongue. **B,** At 8 weeks, the tongue has been depressed and the palatine shelves are elevated but not fused. **C,** Fusion of the shelves and the nasal septum is completed.

Week 12: secondary cartilage

- 3 types
    1. Condylar cartilage
    2. Coronoid cartilage
    3. Symphyseal cartilage
- Condylar cartilage appears at 12 weeks of development and rapidly forms a cone-shaped or carrot-shaped mass that occupies most of the developing ramus
- Mass of cartilage converted to bone via endochondral ossification
- At 20 weeks of development, only a thin layer of cartilage remains in the condylar head

Primary cartilage	**Meckel's Cartilage**	**7 Weeks** - Ossification commences at inferior alveolar nerve point of division - Continues anterior and posterior from this point
Secondary cartilages	Condylar (most important secondary cartilage)	**12 weeks** **-** Appears! **20 weeks** - Thin layer remains until 20 years old - Mechanism for growth
	Coronoid Symphysial (2 of them)	

Cleft lip and palate



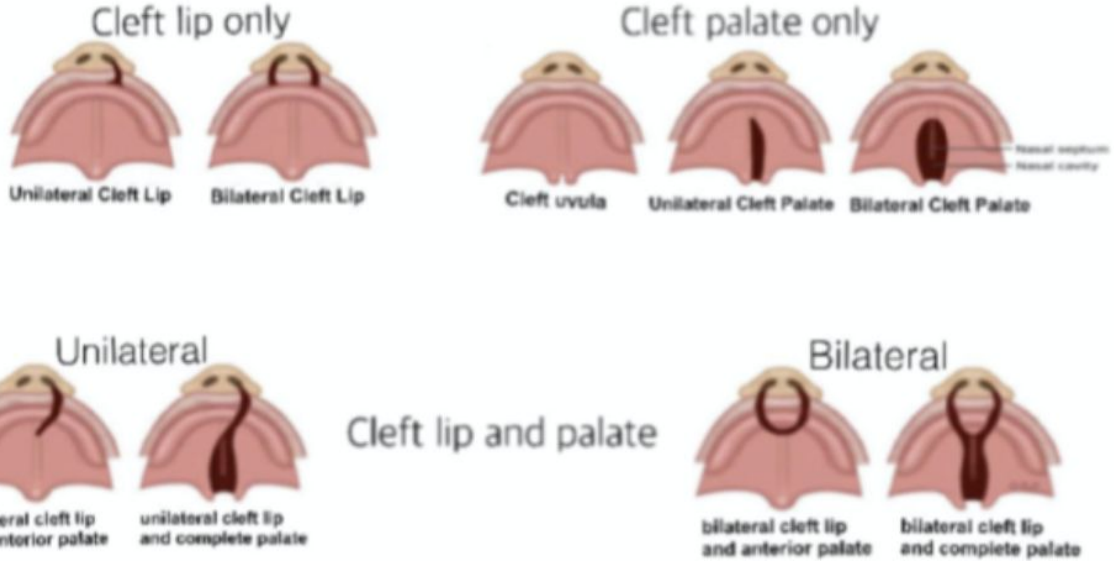
What are characteristic facial features of cleft lip and palate as shown in the diagram?

- Prominent eyes and forehead
- Reduced as lower face grows

When does the interruption in embryonic development occur to cause CLP?

- Between 4th and 10th week of development

Classification of CLP



1. Structures involved
2. Symmetry of expression
3. Severity
4. Isolated (70%) vs. syndromic

CLP Malfunctions

Md cleft: lack of fusion b/w **mandibular processes**

Median cleft lip: lack of fusion b/w **two medial nasal processes**

Bilateral cleft lip: lack of fusion between **maxillary process** and **median nasal process**

Cleft palate: lack of fusion b/w **lateral palatine process, nasal septum** or **medial palatine process**

1. Failure of shelves and septum to contact due to lack of growth, physical disturbance during shelf elevation
2. Failure of epithelium adhesion - no breakdown
3. Rupture after fusion of shelves
4. Defective merging and consolidation of mesenchyme of shelves

Genetics of CLP: Non-syndromic vs Syndromic

Non-syndromic: *Isolated phenotype occurring in absence of any other structural or cognitive abnormalities*

- Genetics + **environmental THRESHOLD**
- MSX1; maintain growth of primary palate through expression of growth factors

Syndromic: *Systemic, multifactorial presentation of phenotypes in different parts of the body*

- Genetics
- Van der Woude syndrome IRF6; single gene mutation

Environmental Interplay of CLP

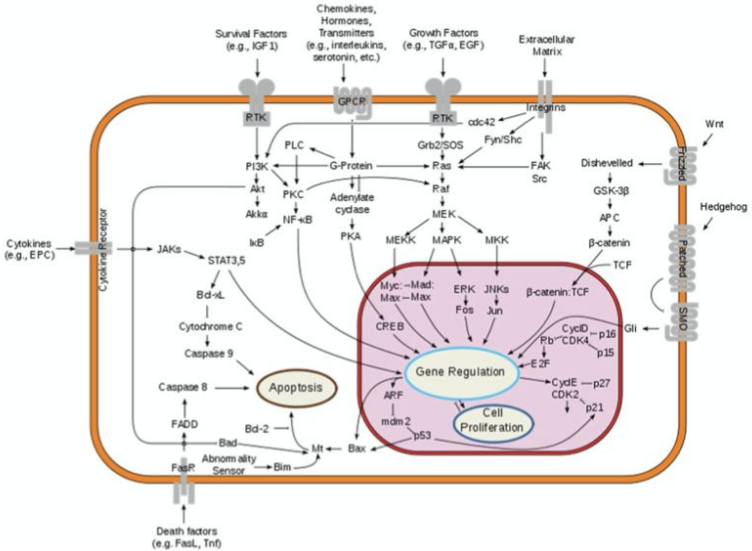
*Caused by **maternal teratogens***

- Alcohol
- Cigarettes
- Drugs and medications
- Nutritional deficiencies - Zn, Folate
- Infectious agent
- X-ray radiation
- Hormones

Example: ADH1C alcohol dehydrogenase

1. Normally reduces ethanol to aldehyde
2. Mutation causes build up of ethanol
3. Competitively inhibits retinoic acid
4. Dysregulation of neural crest migration that give rise to branchial arches

Knock-on-effects



Gene Transcriptional regulators, homeobox genes, hox genes

Molecule Cell signalling issues

Cell Failure of NCC to migrate/differentiate

Tissue Failure of epithelium to degrade; fusion failure

Organ Failure of tongue to descend; palatal process elevation failure

CLP management

Multidisciplinary Care! (KEYWORD) → orthodontist, pediatrician, psychologist, speech pathologist, ENT, GDP, OMFS

Across a long period of time

More involved then just medical care and surgical correction - it's about managing Pnt expectations, family concerns and setting realistic goals…

Management of Pnt and family psychological health – *What do you say to mother who is worried her early trimester smoking when she wasn't aware of pregnancy caused her childs CLP?* **– PCC Implications**

Left untreated CLP has a variety of implications including:

- Pnt being bullied at school?
- Alterations to basic alimentary/physiological processes → deglutition, masication, phonation
- General Psychological/social impacts → **biopsychosocial model**

CLP Treatment

In the 1st year
- Repair of cleft lip and unilateral anterior palate at 3 months
- Repair of cleft palate at 6 months
- Speech, ENT assessment, Dental, Orthodontics

2nd-5th years
- Speech assessment
- Dental review yearly
- If required, soft tissue revision (eg. lip, nose)
- From 5th year onwards, assess the need for nasendoscopy

6th-12th years
- Orthodontics
- Dental
- Possible nasendoscopy. If indicated pharyngoplasty.

13th-18th years
- Orthognathic surgery
- Soft tissue revision

Orthodontist Role

In the 1st year
- Repair of cleft lip and unilateral anterior palate at 3 months
- Repair of cleft palate at 6 months
- Speech, ENT assessment, Dental, Orthodontics

2nd-5th years
- Speech assessment
- Dental review yearly
- If required, soft tissue revision (eg. lip, nose)
- From 5th year onwards, assess the need for nasendoscopy

6th-12th years
- Orthodontics
- Dental
- Possible nasendoscopy. If indicated pharyngoplasty.

13th-18th years
- Orthognathic surgery
- Soft tissue revision

Resources

- Ten cate’s oral histology chapters 2 & 3
- https://www.youtube.com/watch?v=l5iGrX5hIvM

Questions?