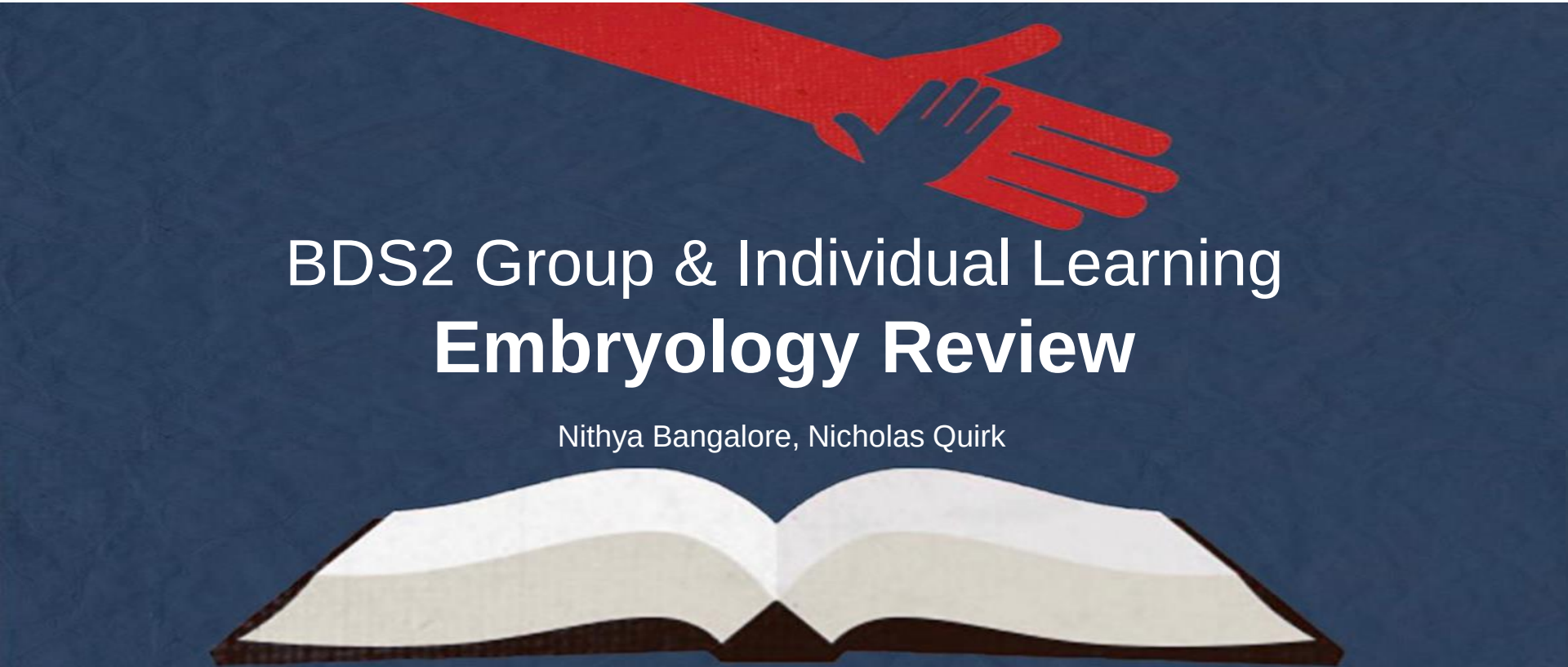
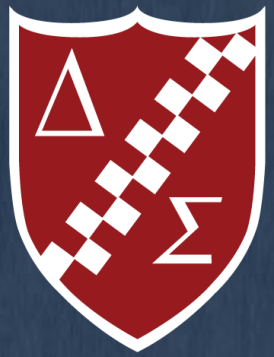


BDS2 Group & Individual Learning

Embryology Review

Nithya Bangalore, Nicholas Quirk

Host and Sponsors



Guild INSURANCE

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ADA SOUTH AUSTRALIA

Embryology Sequence

1. General Embryology
2. Neural Crest Cells (NCCs) and Head Formation
3. Branchial Arch and the Primitive Mouth
4. Formation of the Facial Structures and Primary Palate
5. Formation of the Secondary Palate
6. Formation of the Tongue
7. Development of the skull
8. Development of the Mandible and Maxilla
9. Development of the TMJ

***Note that some of these processes overlap or occur in a slightly different order than above**

Week 1-4

General Embryology

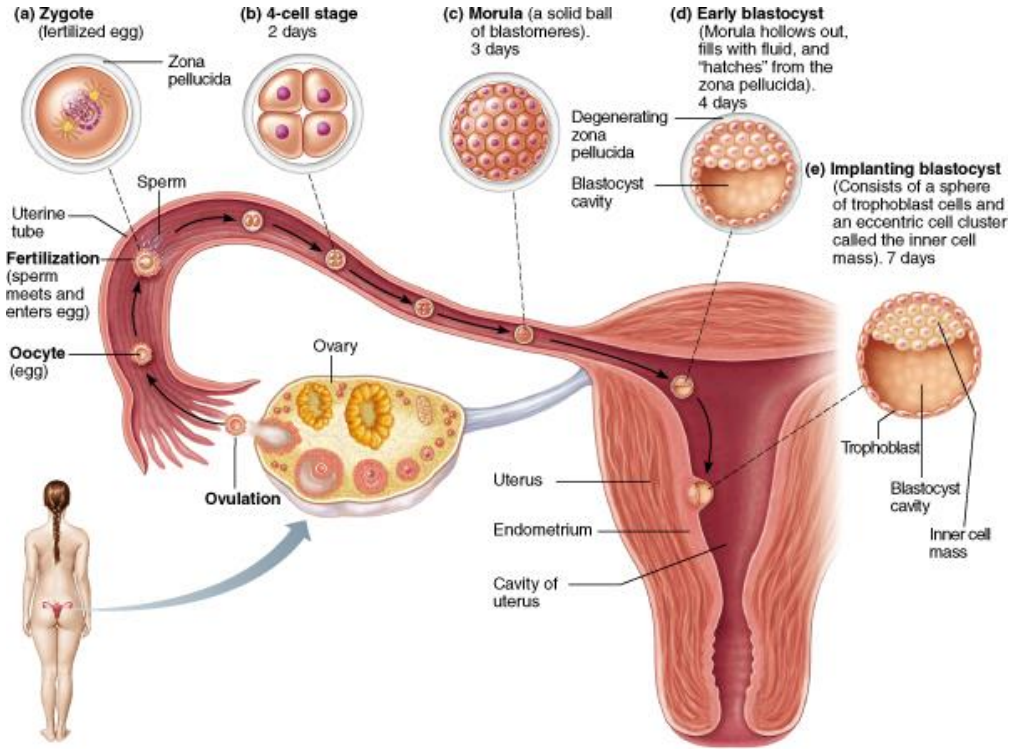
1. Germ Cell Formation and Fertilisation
2. Formation of the Bilaminar Disk
3. Formation of the Trilaminar Disk
4. Formation of the Neural Tube and Fate of the Germ Layers

Week 1

Germ Cell Formation and Fertilisation

- Fusion of male and female germ cells to form zygote
- Congenital defects can occur during the meiosis phase of fertilisation that can affect the normal development of the mouth and teeth i.e. trisomy 21 (Down syndrome) – features of which may include facial clefts, shortened palate, a protruding and fissured tongue and delayed eruption of teeth

Week 1 Cont.


(a) Zygote
(fertilized egg)
Zona pellucida
(b) 4-cell stage
2 days
(c) Morula (a solid ball of blastomeres).
3 days
(d) Early blastocyst
(Morula hollows out, fills with fluid, and "hatches" from the zona pellucida).
4 days
Degenerating zona pellucida
Blastocyst cavity
(e) Implanting blastocyst
(Consists of a sphere of trophoblast cells and an eccentric cell cluster called the inner cell mass). 7 days
Sperm
Uterine tube
Fertilization
(sperm meets and enters egg)
Oocyte
(egg)
Ovary
Ovulation
Uterus
Endometrium
Cavity of uterus
Trophoblast
Blastocyst cavity
Inner cell mass

Week 2

Formation of the Bilaminar Disk

- Phase of rapid proliferation and migration of cells with little or no differentiation of cells
- Cells of the embryoblast differentiate into a two layered disk – endoderm and ectoderm
- Ectoderm (dorsal) – columnar cells that form the amniotic cavity
- Endoderm (ventral) – cuboidal cells that form roof of the secondary yolk sac
- Prochordal Plate - region where the ectoderm and endoderm make contact

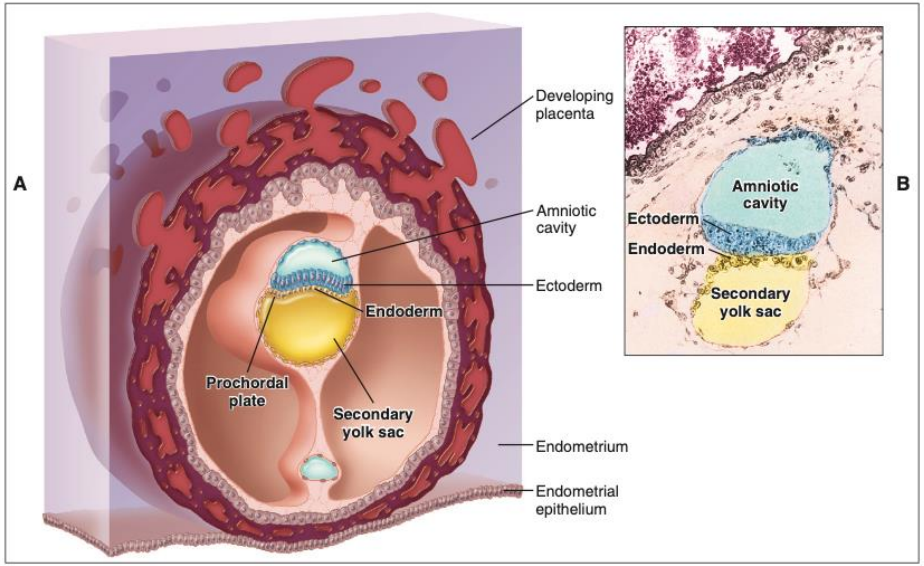


FIGURE 2-6 **A,** Schematic representation and **B,** histologic section of a human blastocyst at 13 days. An amniotic cavity has formed within the ectodermal layer. Proliferation of endodermal cells forms a secondary yolk sac. The bilaminar embryo is well established. (**B,** Adapted from Brewer JI: *Contrib Embryol* 27:85, 1938.)

Week 3

Formation of the Trilaminar Disk (Gastrulation)

- Migration of ectodermal cells rostrally and laterally through the primitive streak
- Ectoderm differentiates to form the neural plate
- The *primitive streak* is formed by the convergence of the neural plate
- Cells of the ectoderm migrate rostrally through the streak and form the notochord
- The notochord supports the primitive embryo
- Cells of the ectoderm also divide and migrate laterally towards the prochordal plate to form the mesoderm

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

Week 4

- Neural tube formation
- Formation of the primitive stomatodeum
- Formation of the branchial arches
- Formation of the tongue

Week 4

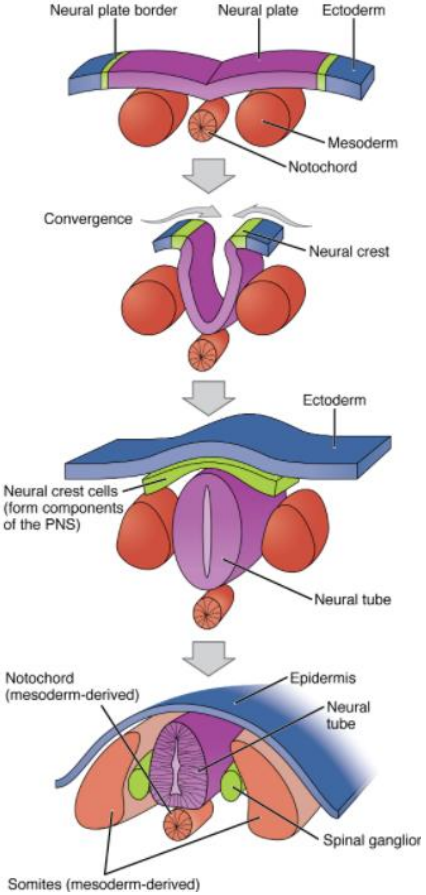
Neural Tube Formation (Neurulation)

1. Thickening within the ectodermal layer at the rostral (head) end if the embryo constitutes the neural plate

2. Borders of the neural plate become raised to form the neural folds and encompass the newly formed neural groove

3. Neural folds converge and eventually fuse to form the neural tube, which separates from the ectoderm.

4. Neural crest cells (NCCs) are cells at the margin of the neural plate that separate during neurulation and undergo **epithelial-mesenchymal** transformation to form many structures, including the majority of CT in the head



Week 4

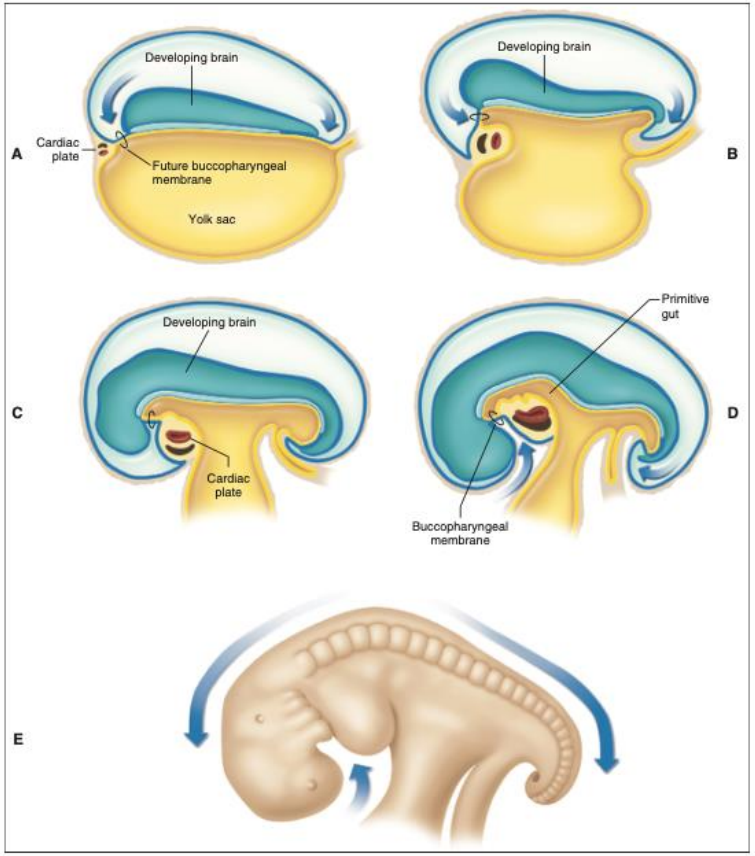
- Treacher Collins syndrome is an example of a deformity caused by improper NCC migration to the facial region
- All the tissues of the tooth (except enamel and some cementum) and supporting structures are derived direct from NCCs and failure of migration can prevent proper dental development

Week 4

Folding of the Embryo and Formation of the Primitive Stomatodeum

- Folding along the **rostro-caudal** axis (head to tail) and lateral axis
- Primitive stomatodeum (oral cavity) formed by the head fold and is separated from the gut by the buccopharyngeal membrane

https://www.youtube.com/watch?v=yXUv4MPuNTA

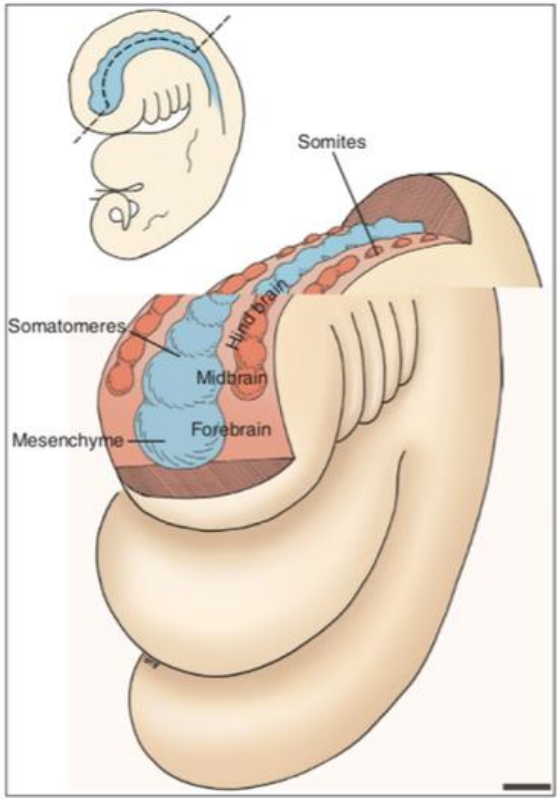


Week 4

Branchial Arch Formation

- Formation of the forebrain, midbrain and hindbrain during folding

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



Week 4

Branchial Arch Formation cont.

- NCCs migrate from the midbrain and rhombomeres to form certain branchial arches
- These branchial arches will be the precursor to structures of the head and neck
- Transcription factor genes (e.g Homeobox genes) are integral to regulating NCC migration and have a role in regulating dental development

Midbrain, rhombomere 1 and 2	**1st wave** Face Connective Tissue
	2nd wave Formation of jaw Branchial arch 1
Rhombomere 4	Branchial arch 2
Rhombomere 6	Branchial arch 3
Rhombomere 8	Branchial arch 4

Week 4

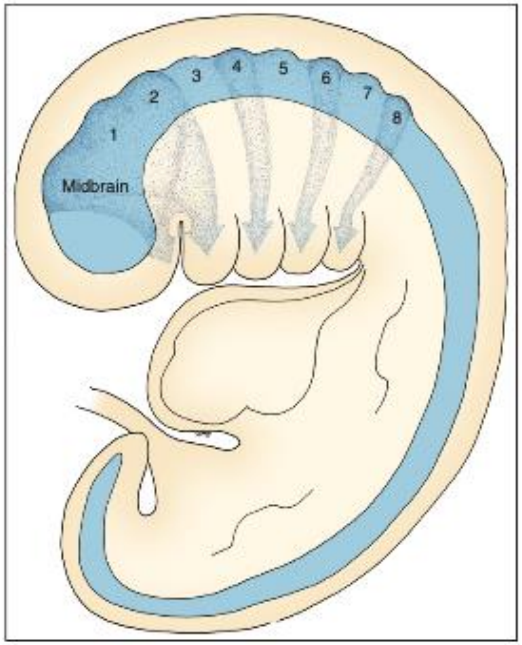
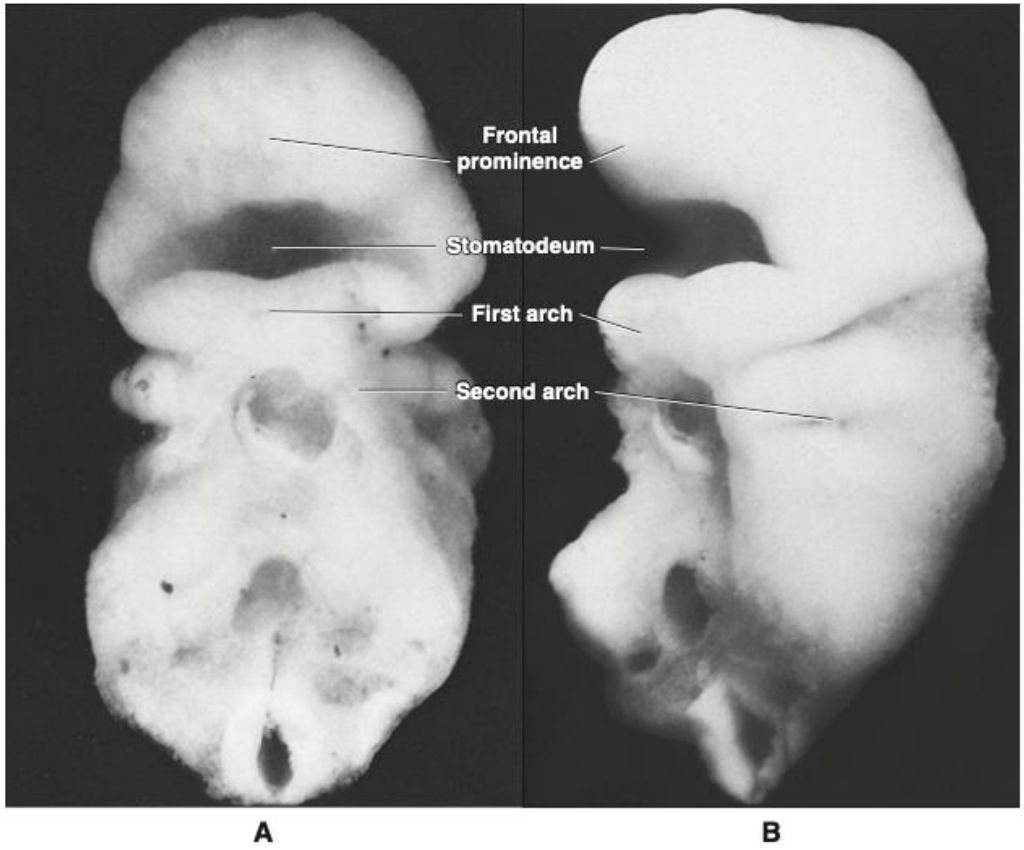


FIGURE 3-4 The source and pattern of neural crest migration to the developing face and branchial arch system. The midbrain and rhombomeres 1 and 2 contribute to the face and first branchial arch.

Week 4



A 26-day old embryo

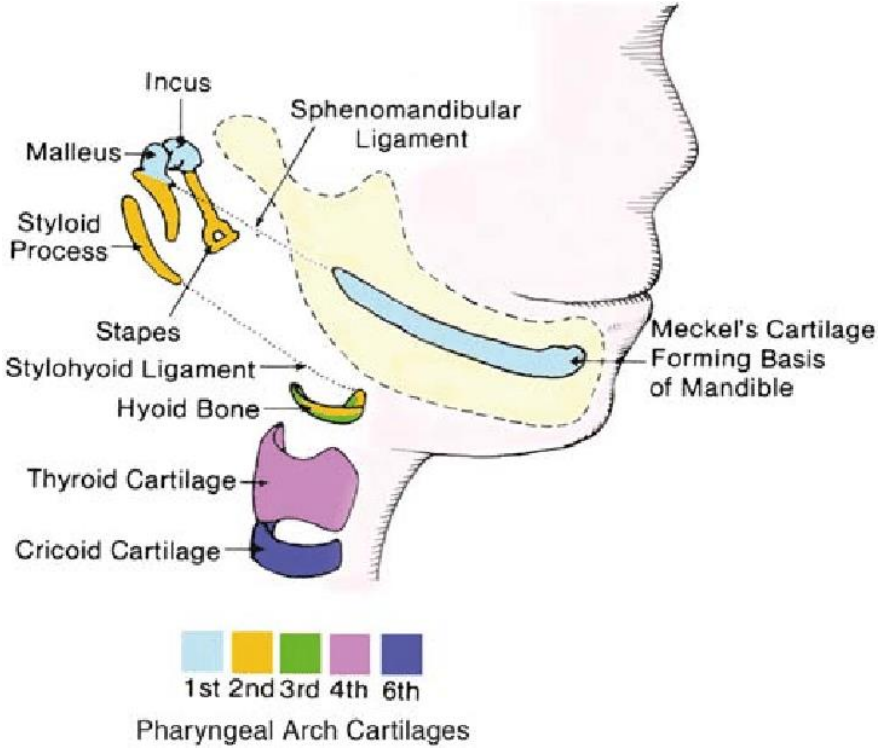
Week 4

TABLE 3-1

Derivatives of the Branchial (Pharyngeal) Arch System

	ARCH	GROOVE	POUCH
First	1. Mandible and maxilla 2. Meckel's cartilage: a. Incus and malleus of inner ear b. Sphenomalleolar ligament c. Sphenomandibular ligament	1. External auditory meatus	2. Tympanic membrane 3. Tympanic cavity 4. Mastoid antrum 5. Eustachian tube
Second	1. Reichert's cartilage: a. Styloid process of temporal bone b. Stylohyoid ligament c. Lesser horns of the hyoid bone d. Upper part of the body of the hyoid bone	Obliterated by the down-growth of the second arch	1. Largely obliterated 2. Contributes to tonsil
Third	1. Lower part of the body of the hyoid bone 2. Greater horns of the hyoid bone		Inferior parathyroid gland Thymus
Fourth	1. Cartilages of the larynx		Superior parathyroid gland Ultimobranchial body
Fifth	Transient	Transient	Transient
Sixth	Transient	Transient	Transient

Week 4


Incus
Sphenomandibular Ligament
Malleus
Styloid Process
Stapes
Stylohyoid Ligament
Hyoid Bone
Thyroid Cartilage
Cricoid Cartilage
Meckel's Cartilage Forming Basis of Mandible
1st 2nd 3rd 4th 6th
Pharyngeal Arch Cartilages

Week 4

TABLE 3-2

Innervation and Vascularization of Pharyngeal Arches

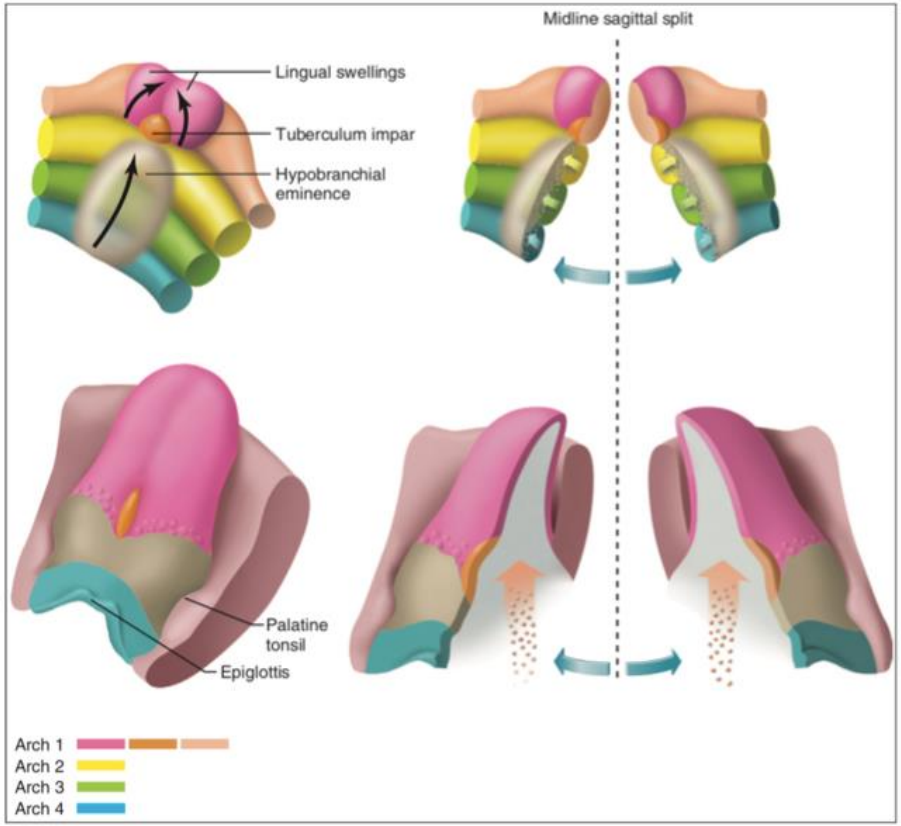
ARCH	BLOOD VESSEL	NERVE
First	First aortic arch	Mandibular (and maxillary) division of the trigeminal nerve (cranial nerve V)
Second	Second aortic arch	Facial (VII)
Third	Third aortic arch	Glossopharyngeal (IX)
Fourth	Fourth aortic arch	Vagus (X)

Week 4

Development of the Tongue

- Begins at 4 weeks of gestation and is completed at week 7
- Pharyngeal arches 1, 2 and 3 meet at the midline beneath the primitive mouth
- **Mucous membrane of the anterior 2/3 of the Tongue -** Formed by the merging of the **Tuberculum impar** and **lateral lingual swellings** (which initially flank either side of the impar)
- **Root of the tongue –** Formed by A large swelling consisting of the **copula (second arch)** and **hypobranchial eminence (third and fourth arches)**
- As the tongue develops the hypobranchial eminence overgrows the copula which disappears
- The posterior part of the 4th arch marks the development of the epiglottis

Week 4


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

Week 4

Development of the Tongue cont.

- The tongue separates from the floor of the mouth by a down growth of ectoderm around its periphery
- This then degenerates to form the lingual sulcus and gives rise to tongue mobility
- Muscles of the tongue arise from **occipital somites,** which migrate forward into the tongue area-> hence is supplied by the hypoglossal nerve (CN XII)

Part of Tongue	Branchial Arch that it's derived from	…Therefore it's nerve supply
Anterior 2/3	Branchial Arch 1	CN V – Trigeminal
Posterior 1/3	Branchial Arch 3	CN IX – Glossopharyngeal
Muscular innervation	Occiptial Somites (not a branchial arch)	CN XII – Hypoglossal

Week 5

Fusion of Processes

- The formation of the face is described in terms of formation and fusion of several processes and processes

Olfactory Placode and Nasal Process Development (Day 28)

- **olfactory placode formation –** localised thickenings develop within the ectoderm of the frontal prominence (above opening of stomatodeum)
- Rapid proliferation of mesenchyme around the placodes create a horseshoe-shaped ridge that forms the nasal pit
- The lateral arm of the horseshoe is called the lateral nasal process and and the mesial arm is called the medial nasal process

Week 5

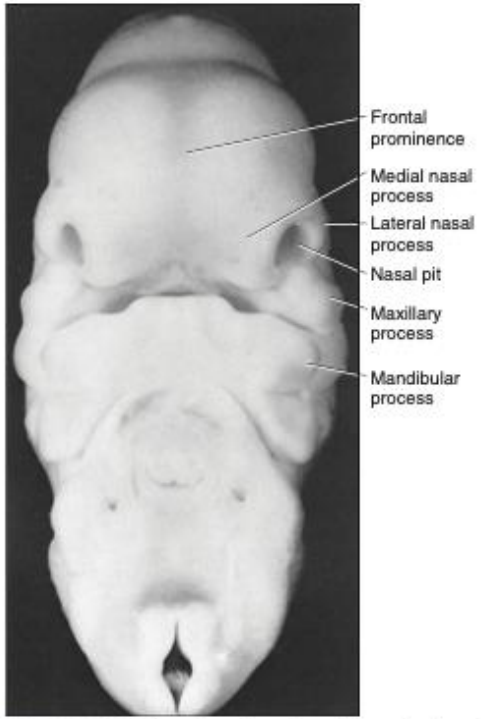


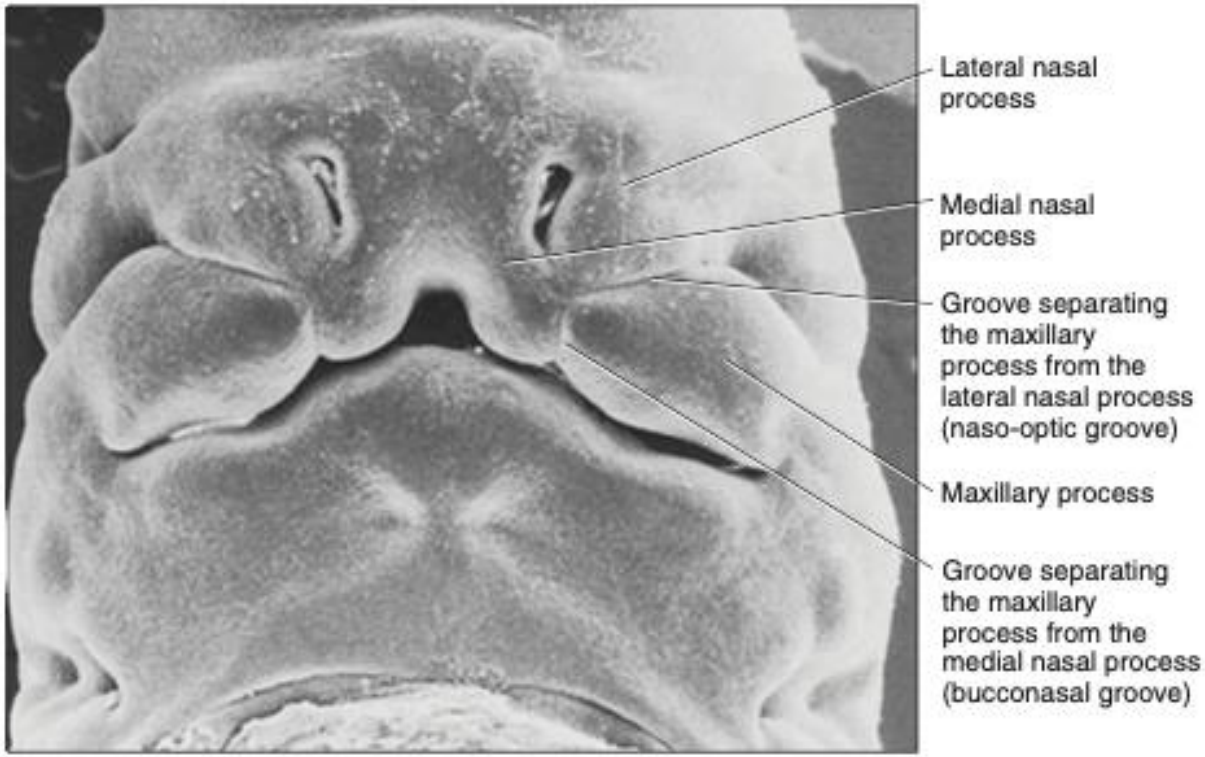
FIGURE 3-13 A 34-day-old embryo viewed from the front. The nasal pits have formed, thereby delineating the lateral and medial nasal processes. (Courtesy of H. Nishimura.)

A 35-day old embryo

Week 6

1. Upper Lip and Philtrum
2. Primary Palate and Anterior Maxilla
3. Lateral parts of the Upper Lip
4. Lower Lip
5. Formation of the Mandible

Week 6


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)

Week 6

Upper Lip, Philtrum, Primary Palate and Anterior Maxilla Formation

- Mx process grows medially and approaches medial and lateral nasal processes, but remains separate from them (separated by bucconasal and nasolacrimal grooves)
- Medial nasal processes then grow towards the midline and merge together to form the middle portion of the upper lip/philtrum, the anterior portion of the maxilla and the primary palate

Lateral part of Upper Lip Formation

- Fusion between the anterior portion of the Mx process and the lateral aspect of the medial nasal process will obliterate the bucconasal groove to form the lateral aspects of the upper lip

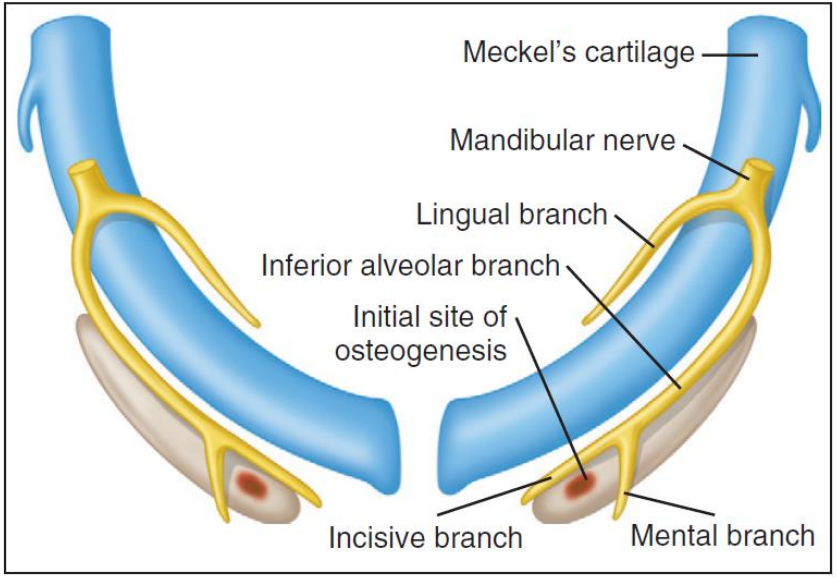
Lower Lip Formation

- The merging of the mandibular processes at the midline form the lower lip

Week 6

Formation of the Rudimentary Mandible

- Begins at week 6
- Meckel's cartilage (hyaline) present and separated in midline by mesenchyme
- Cartilage extends to developing ear region
- Mandibular nerve (CN V) begins 2/3 of the way up the cartilage and then almost immediately divides into IAN and lingual nerves
- These nerves run along the medial and lateral aspects of the cartilage respectively
- The IAN will further divide into the incisor and mental branch more anteriorly



Week 7

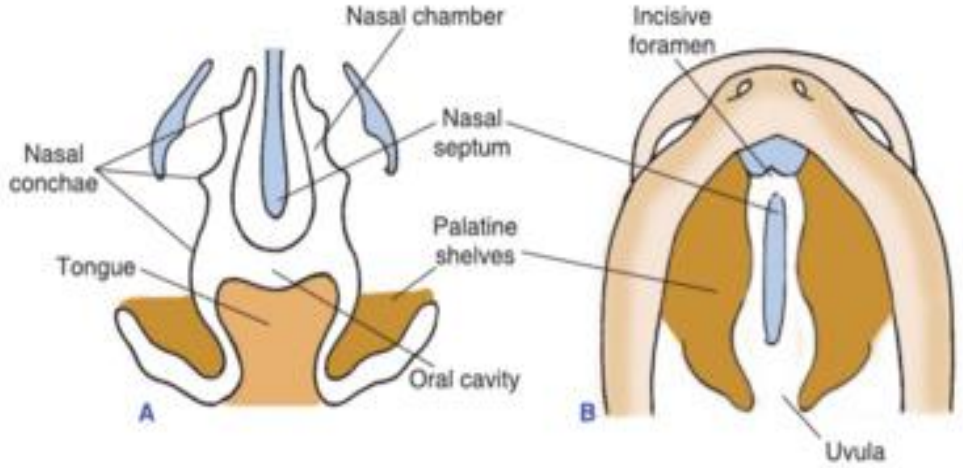
Formation of the Rudimentary Mandible cont.

- Intramembranous ossification begins at week 7
- Occurs at the condensation between the splitting of the IAN into the incisal and mental branch
- Bone formation occurs rapidly and spreads anteriorly and posteriorly from the midline to the point of the Md nerve splits into the lingual and IAN
- Two areas of ossification remain separated until mandibular symphysis occurs shortly after birth
- Ramus develops from rapid ossification posteriorly and upwards into the mesenchyme of the first arch
- The ‘turn’ in direction Is marked by the lingual
- Meckel’s cartilage gives rise to the incus and malleus of the ear and the sphenomandibular ligament, however the remaining structure disintegrates
- At **10 weeks** of development the rudimentary mandible is formed

Week 7

Secondary Palate Formation

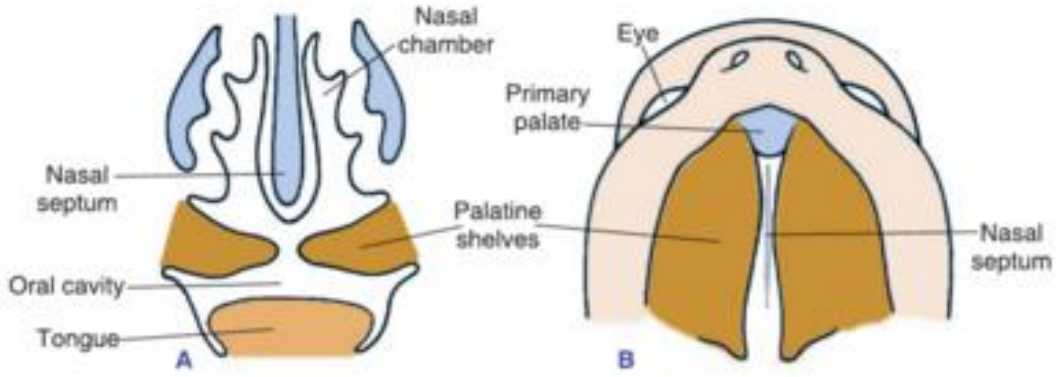
- Nasal septum grows downwards
- Palatine shelves emerge from maxillary processes
- Shelves grow downwards, obliquely towards either side of the tongue



Week 8

Formation of the Secondary Palate

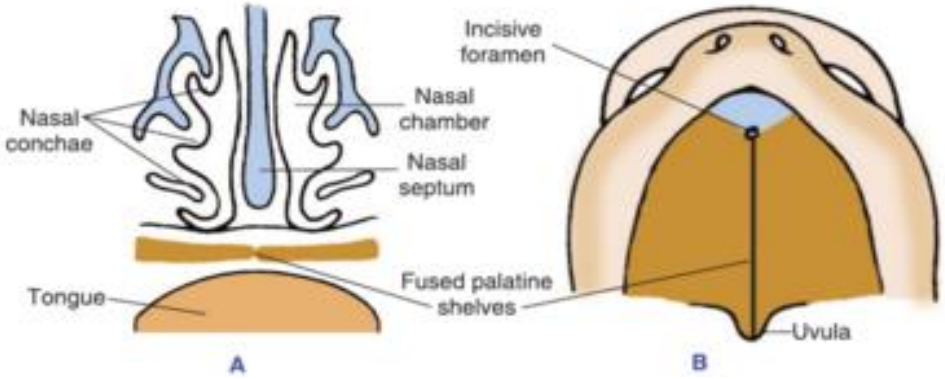
- Tongue descends and moves away from the shelves
- The shelves ascend and merge with the primary palate
- Palatine shelves move towards each other and fuse with the nasal septum – fused along the midline from anterior to posterior
- Nasal and oral cavities separated



Week 9

Fusion of the Palatine Shelves (True Fusion)

- Epithelium is eliminated as two shelves meet
- Midline epithelial seal is formed -> seam breaks down for growth creating islands of epithelium
- Epithelial cells differentiate into mesenchymal cells
- This step is a pre-requisite of NCC migration



Week 12 – Secondary Cartilage

We saw starting from week 6 the formation of the body and ramus of the Mandible

The further growth of the Md until birth is influenced strongly by the appearance of 3 secondary growth cartilages (1. Condylar cartilage, 2. coronoid cartilage and the 3. Symphyseal cartilage) and the development of muscular attachments

The Condylar Cartilage

1. At week 12 the condylar cartilage rapidly forms a cone shaped mass that occupies most of the developing ramus

2. The cartilage is quickly converted to bone by endochondral ossification

3. At 20 wees only a thin layer of cartilage remains in the condylar head

Note that the secondary cartilage has a different histological structure than that of the primary Meckel's cartilage. Secondary cartilage has larger cells and less intercellular matrix formed

Review Video

https://www.youtube.com/watch?v=FhhWG3XzARY

Embryological Malfunctions

i.e cleft lip

Cleft Lip and/or Palate (CLP)

Causes:

- Environmental factors

1. Infectious agents (rubella virus)
2. X-ray radiation
3. Drugs (nicotine, alcohol)
4. Hormones
5. Nutritional deficiencies (

Note: if teratogen exerts effect before 4 weeks of gestation, embryo death is most likely. CLP occurs due to malformation during weeks 4-8 of gestation during the period of morphogenesis and histodifferentiation.

These causes will alter differing pathways that correspond with CLP; however commonly cytokines that are involved in growth or fusion of tissues are major functions effected.

Good ones to remember:

- TGFβ (transforming growth factor beta) superfamily molecule genetic mutations (family includes BMP's)
- Shh gene (Sonic Hedgehog) encodes proteins for cell-cell interaction and required for palate / frontonasal development
- FGF (Fibroblast growth factor) targets Shh
- Msx1 (homeobox gene) regulates outgrowth of Mx prominences
- IRF6 (interferon regulatory factor 6) lacking leads to disrupted epithelial development and possibl involved in TGFβ signalling

A. Despande and S. Goudy 2019 'Cellular and molecular mechanisms of cleft palate development'

Cleft Lip (Week 6)

Types of Cleft Lip and Malfunctions

Oblique facial cleft: lack of fusion between the maxillary process and lateral nasal process

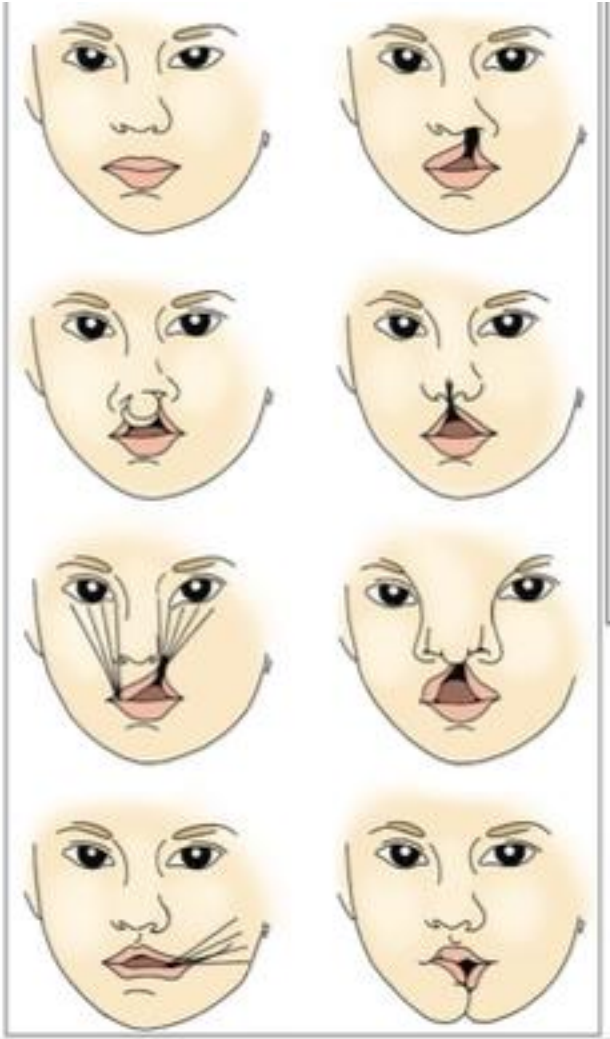
Median cleft lip: lack of fusion between the two medial nasal processes

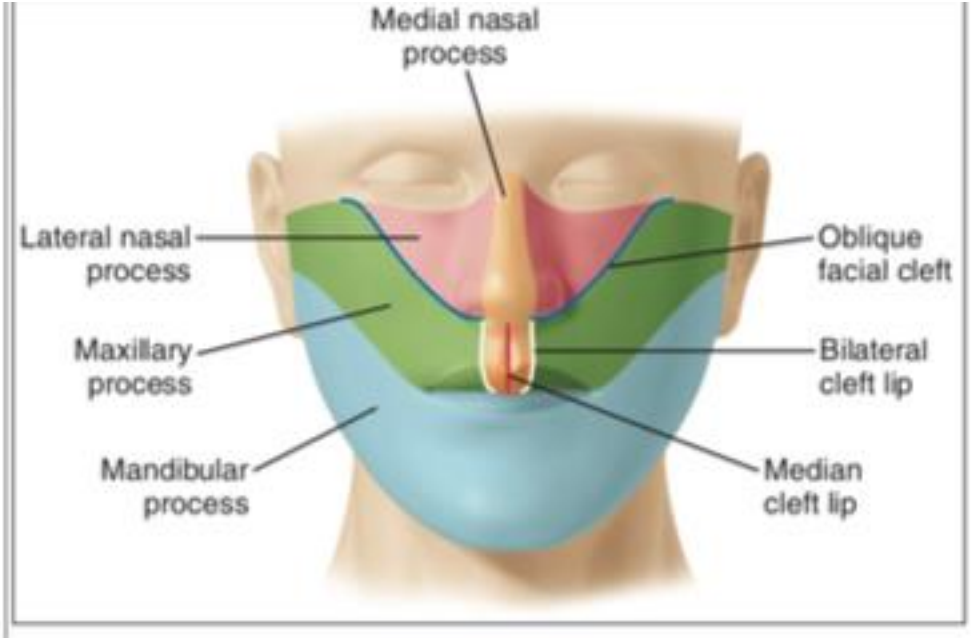
Bilateral cleft lip: lack of fusion between the maxillary processes and median nasal processes

Microstomia: excessive merging of the mandibular and maxillary processes

Macrostomia: resulting from failure of the maxillary and mandibular processes to fuse

Mandibular cleft: Failure of Md processes to fuse





A, Normal. **B,** Unilateral cleft lip. **C,** Bilateral cleft lip. **D,** Median cleft lip. **E,** Oblique facial cleft. **F,** Median cleft (frontonasal dysplasia). **G,** Lateral facial cleft. **H,** Mandibular cleft.

Cleft Palate

Note: usually occurs together with cleft lip

Cleft Palate w/ Facial Cleft: Occur when clefts of the lip and anterior Mx occur which subsequently prevents the palatine shelves making contact as well

Cleft palate w/o facial cleft: Occur either from

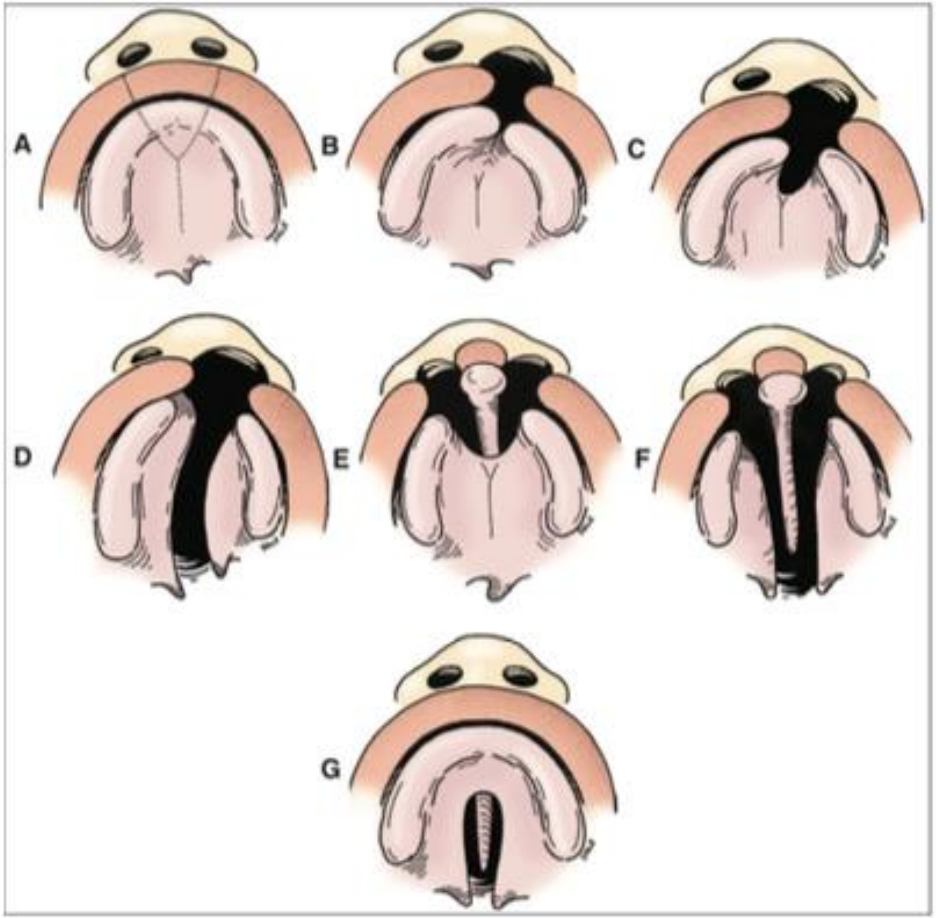
1. Failure of the shelves and septum to contact each other

2. Failure of the shelves and septum to fuse

3. Rupture after fusion of the shelves has occurred

4. Defective merging and consolidation of the mesenchyme of the shelves

Note that the extent of clefting reflects the time when the processes involved in closure of the secondary palate have been affecting i.e. Full clefting = interference at the start of closure and partial clefting = interference later in the process



A, Normal. **B,** Cleft of lip and alveolus. **C,** Cleft of lip and primary palate. **D,** Unilateral cleft lip and palate. **E,** Bilateral cleft lip and primary palate. **F,** Bilateral cleft lip and palate. **G,** Cleft palate only.

CLP Treatment

CLP Treatment Managment

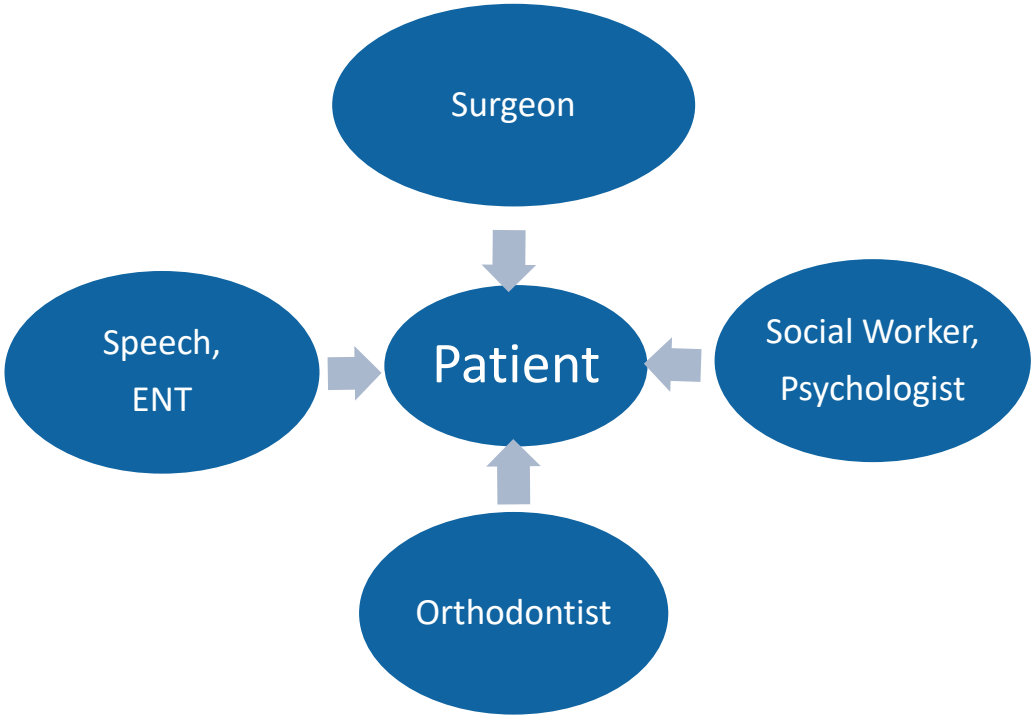
Multidisplinary Care!

Across a long period of time

More involved then just medical care and surgical correction

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**

Management of pnt being bullied at school?



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

Questions?

More Sources

- Read Ten Cates Chapter 2 and 3!!!!
- https://www.youtube.com/watch?v=l5iGrX5hIvM (Honestly the best video you will watch on embryo – it will teach you pretty much everything you need to know on the topic)