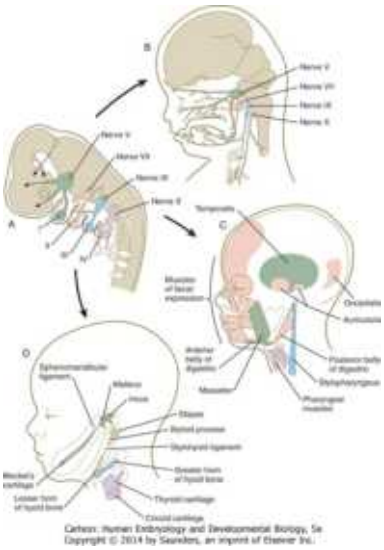
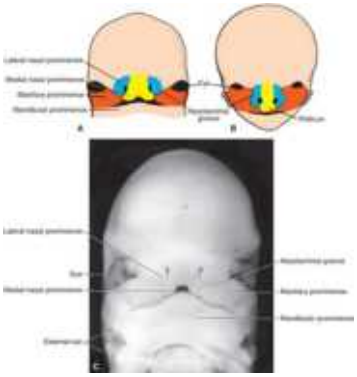
Embryology of the Head and Neck

Monika Gooz, MD, PhD
Associate Professor
Department of Regenerative Medicine and Cell Biology
Basic Science Building (BSB), Room 615C
Email: beckm@musc.edu
Office Phone: (843) 876-2363



Lecture Outline

1. **Introduction**
   - Overview of craniofacial embryology
   - Clinical relevance and developmental milestones
2. **Basic Patterning of the Head and Neck**
   - Early morphogenesis and germ layer contributions
   - Segmental organization of the craniofacial region
3. **Development of Craniofacial Structures**
   - Formation of the face and jaws
   - Palatal development and fusion
   - Development of the nose and olfactory system
4. **Craniofacial Malformations**
   - Common anomalies and their embryological basis
   - Syndromic vs. isolated defects
5. **Development of the Pharynx and Its Derivatives**
   - Pharyngeal arches: structure and derivatives
   - Pharyngeal grooves and their fate
   - Pharyngeal pouches and organogenesis
6. **Initial Development of the Pituitary Gland**
   - Dual origin and integration of Rathke's pouch and infundibulum
7. **Development of the Tongue**
   - Contributions from pharyngeal arches
   - Innervation and muscular development
8. **Malformations of the Pharynx and Its Derivatives**
   - Clefts, fistulas, and other congenital anomalies
   - Diagnostic and clinical implications



Reading Assignments:

Text: Langman's Medical Embryology, 14th or 15th ed. by Sadler *Ch. 17*

Learning Objectives:

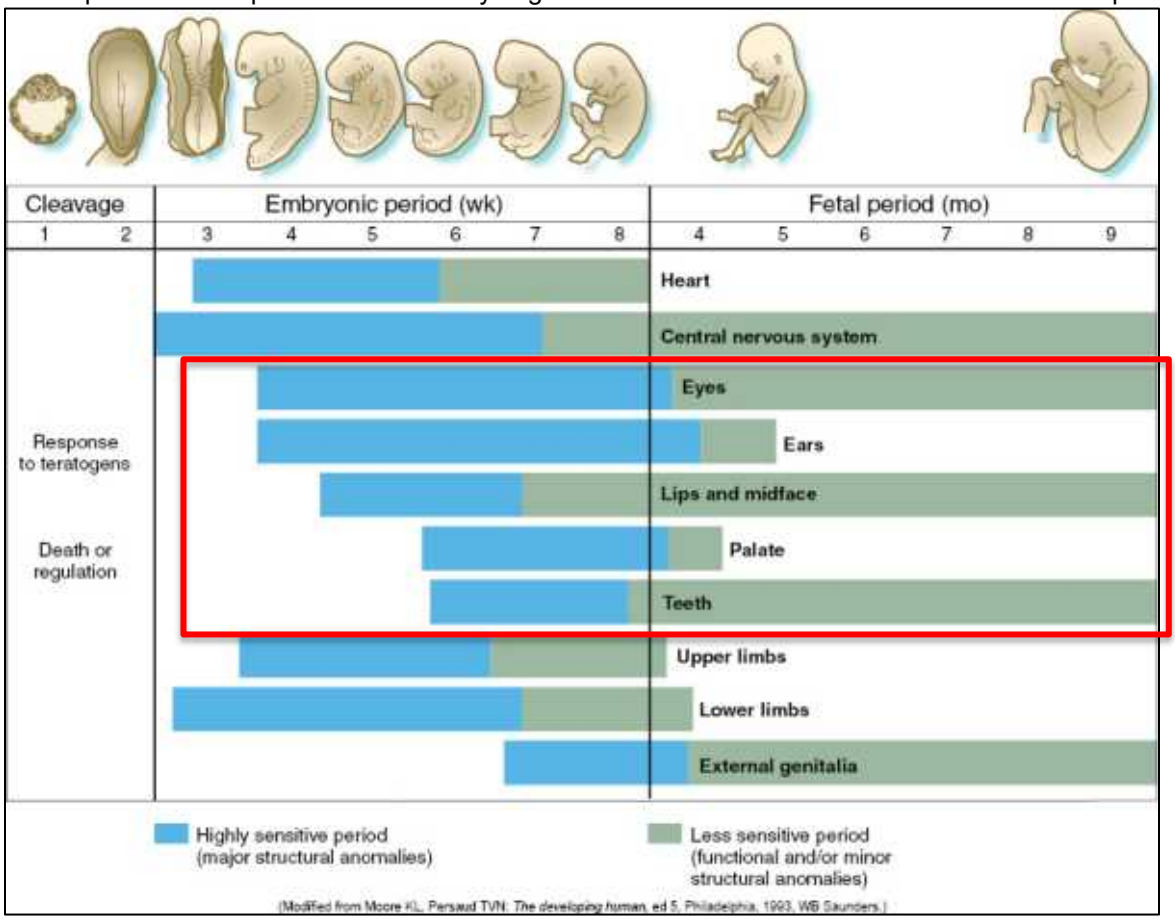
By the end of this lecture series, students will be able to:

- **Distinguish between the two types of cranial and pharyngeal bone derivatives** - membranous and cartilaginous - and identify the head and neck structures derived from each.
- **Describe the five facial primordia,** including the frontonasal prominence, paired maxillary prominences, and paired mandibular prominences.
- **Explain the formation of the nasolacrimal duct and intermaxillary segment,** detailing the roles of the facial primordia involved.
- **Differentiate between ectodermal and endodermal epithelial boundaries** within the oral cavity and understand their developmental limits.
- **Outline the tissue origins and developmental processes of the primary and secondary palates,** including fusion events and structural contributions.
- **Identify the embryological causes of cleft lip and cleft palate**, focusing on the failure of fusion between specific facial prominences and palatal shelves.
- **Describe the germ layer derivatives**—ectoderm, mesoderm, endoderm, and neural crest—for the four main components of the pharyngeal arches. (*continued on next page*)

- **Detail the derivatives of the first, second, third, fourth, and sixth pharyngeal arches**, including associated cranial nerves, muscles, skeletal elements, ligaments, and aortic arch arteries.
- **Explain the dual tissue contributions to the pituitary gland**, including Rathke's pouch (oral ectoderm) and the infundibulum (neuroectoderm).
- **Describe the pharyngeal arch contributions to tongue development**, including muscular and sensory innervation origins.
- **Recognize common anomalies of tongue development**, such as ankyloglossia and bifid tongue.
- **Identify major malformations of the pharynx and its derivatives**, including branchial cleft cysts, fistulas, and other congenital anomalies.

INTRODUCTION

You will examine the developmental pathways of the face, palate, tongue, and cranium, and explore how these structures emerge through the coordinated contributions of all three germ layers—ectoderm, mesoderm, and endoderm. Emphasis will be placed on the embryological mechanisms and clinical relevance of these processes.



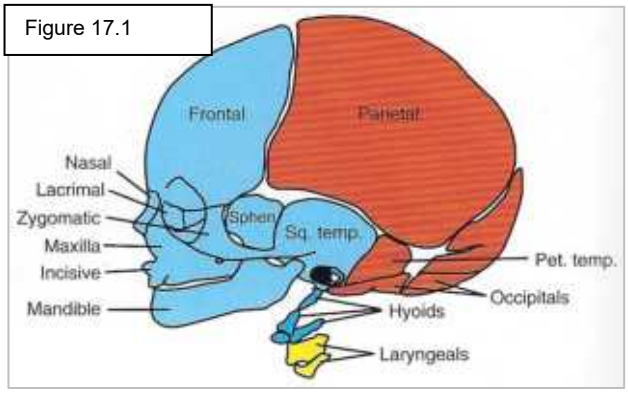
When examining the developmental timeline across various organ systems, we observe distinct periods associated with the formation of specific features in the head and neck region. Importantly, development of the central nervous system (CNS) spans the entire nine-month gestational period and continues into the formative years after birth. While each system follows its own developmental trajectory, the third to eighth weeks of gestation represent the most vulnerable window for teratogenic events affecting neural development.

Development of the CNS spans the entire 9-month period and into the formative years after birth.

BASIC PATTERNING

The axial skeleton—including the skull, vertebral column, ribs, and sternum—develops from three embryonic sources: paraxial mesoderm, lateral plate mesoderm, and neural crest cells. From the occipital region of the head down to the sacral region of the lower body, the paraxial mesoderm forms paired, condensed (epithelialized) mesenchymal structures on either side of the developing neural tube known as **somites**. In the cranial region, mesenchyme located anterior to the occipital somites condenses into structures called **somitomeres**, which are similar to somites but are more loosely organized (unsegmented).

Figure 17.1

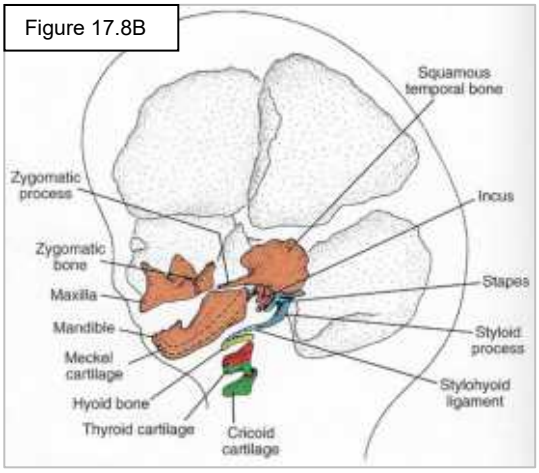


Consequently, the bones of the face and skull are derived from a combination of somitomeres, occipital somites, and neural crest cells. *Figure 17.1* illustrates the tissue origins of various skeletal structures:

- **Blue** indicates neural crest-derived elements
- **Red** represents paraxial mesoderm derivatives (somites and somitomeres)
- **Yellow** denotes contributions from lateral plate mesoderm

Craniofacial region
(skull and face)
- Paraxial mesoderm
- Lateral plate mesoderm
- Neural crest cells

Figure 17.8B



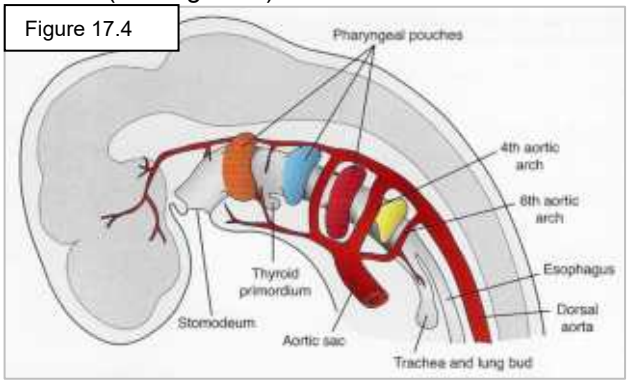
The bony structures of the head and neck develop through two distinct processes: **intramembranous ossification** and **endochondral ossification**. These processes give rise to the **neurocranium**, which encases the brain, and the **viscerocranium**, which forms in association with the pharyngeal arches and surrounds the oral cavity, pharynx, and upper respiratory tract (*see Figure 17.8B*). Both regions contain centers of intramembranous and endochondral (cartilaginous) ossification.

Neurocranium encloses the brain.

Viscerocranium develops associated with the pharyngeal arches. It surrounds the oral cavity, the pharynx and upper respiratory tract.

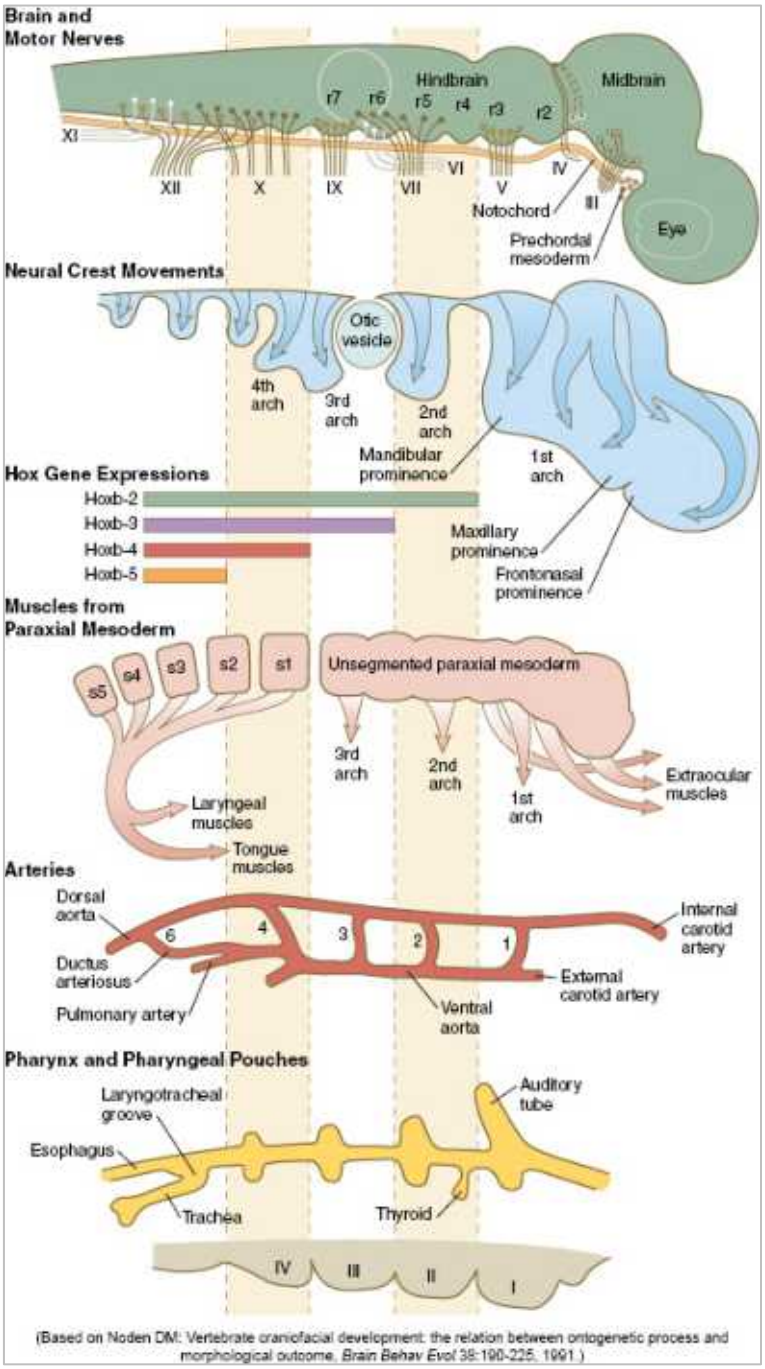
Both regions above have bone development by:
- **Intramembranous ossification**
- **Endochondral ossification**

Figure 17.4



We begin by examining the basic organization of the **pharyngeal arch region** of the human embryo at the end of the first month (*Figure 17.4*). Note the segmental arrangement of the paired arches. Each arch is associated with specific arteries, nerves, muscles, and skeletal elements. Importantly, humans do not possess a fifth pharyngeal arch. This segmental pattern reflects the spatial expression of **Hox genes**, which guide regional identity during development (*see next page*).

Each arch has specific:
- Arch arteries
- Nerves
- Muscles
- Skeletal structures



(Based on Noden DM: Vertebrate craniofacial development: the relation between ontogenetic process and morphological outcome. *Brain Behav Evol* 38:190-225, 1991.)

In *Figure 14-3* from Carlson's *The Developing Human*, various developmental structures—such as nerves, arteries, and gene expression domains—are shown in register with one another. This alignment illustrates that each indicated region of the developing head, in this case a 30-day-old embryo, is associated with specific nerves, genes, and other key components.

Understanding which structures correspond to the same pharyngeal arch is essential. These associations will be revisited throughout the lecture where relevant. While the figure effectively demonstrates the spatial relationships among these elements, the detailed information you'll need is provided in the following pages of notes.

As emphasized previously, **Hox genes** play a critical role in patterning the head region. However, be sure to note the area where Hox gene influence is absent—this distinction is important for understanding regional identity and developmental outcomes.

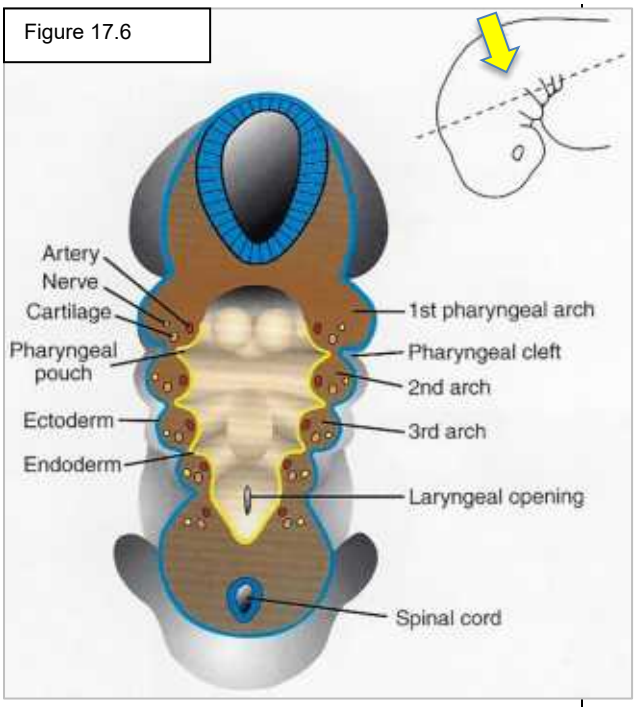
There are **specific components associated** with each arch region as well as cranially to the first arch.

Hox homeobox proteins are important for patterning in the head region. **Note there is no Hox expression cranially to the first arch.**

(Yes, that's all you need to know from this figure.)

Figure 17.6 illustrates a cross-sectional view of the head region in a 5-week-old human embryo, highlighting three of the five pairs of pharyngeal arches. Each arch is lined *internally* by **endoderm** and *externally* by **ectoderm**, forming bilateral structures known as **pharyngeal pouches** and **pharyngeal grooves**, respectively. It is important to note that midline structures—such as the laryngeal opening—are located within the pharyngeal region but are not directly associated with any specific pharyngeal arch.

Figure 17.6



Pharyngeal Arches central mesenchymal mass from:

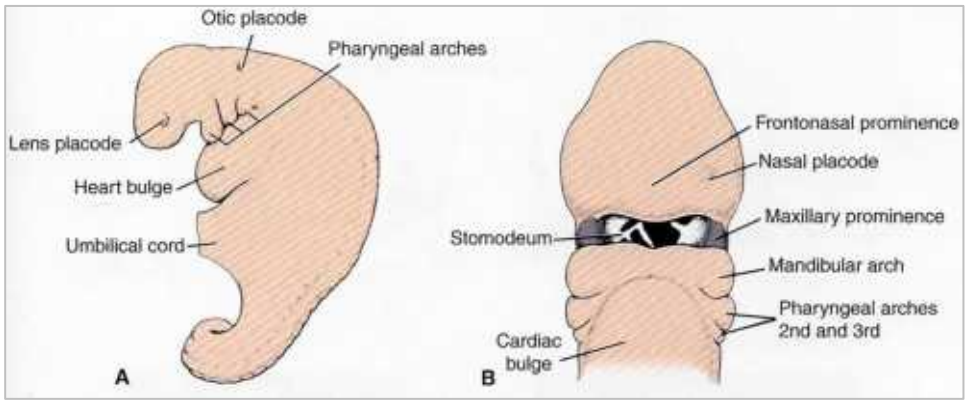
- Paraxial mesoderm
- Neural crest cells

and…

- Surrounded by pouches and grooves

Pharyngeal arches are characterized by a central mesenchymal core composed of **paraxial mesoderm** and **neural crest cells**, surrounded by the aforementioned pouches and grooves. Within this mesenchymal mass, distinct components—including **arch arteries**, **muscles**, **nerves**, and **skeletal elements**—will differentiate and contribute to the structural and functional organization of the head and neck. These developmental processes will be explored further in the second hour of the lecture.

At this stage of development, the **paraxial mesoderm**, **lateral plate mesoderm** (also referred to as **prechordal plate mesoderm**), and **neural crest cells** are actively forming mesenchyme and beginning to contribute to



the developing cranial and facial regions. These early contributions lay the foundation for the complex morphogenesis of the head and face.

Craniofacial region

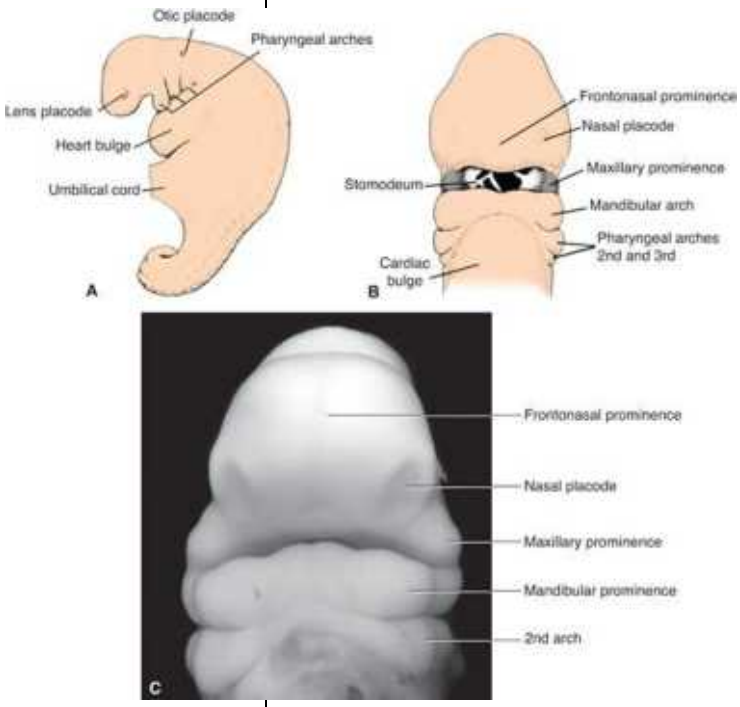
- Paraxial mesoderm
- Lateral plate mesoderm (also called prechordal plate mesoderm)
- Neural crest cells

The **craniofacial region**—with its diverse embryological origins and intricate patterning—will be the primary focus of the **first hour of this lecture**.

DEVELOPMENT OF THE CRANIOFACIAL REGION

(Side bar notes for this section are on the next page)

We will primarily focus on the **superficial ectoderm** and the organization of facial prominences—also referred to as "processes" in some textbooks. These prominences either fuse or fail to fuse with adjacent structures, a process that is critical to normal facial development. In certain cases, deeper structures beneath the surface will also be discussed due to their clinical significance. The **stomodeum**, a central depression on the embryonic face, serves as a key morphological reference point (*see figures below*).
Much of the **facial mesenchyme** is derived from **neural crest cells**, particularly in the **frontonasal region**. The **lower face** originates from the **first pharyngeal arch**, which gives rise to the **maxillary** and **mandibular prominences.**



The Five Facial Primordia:

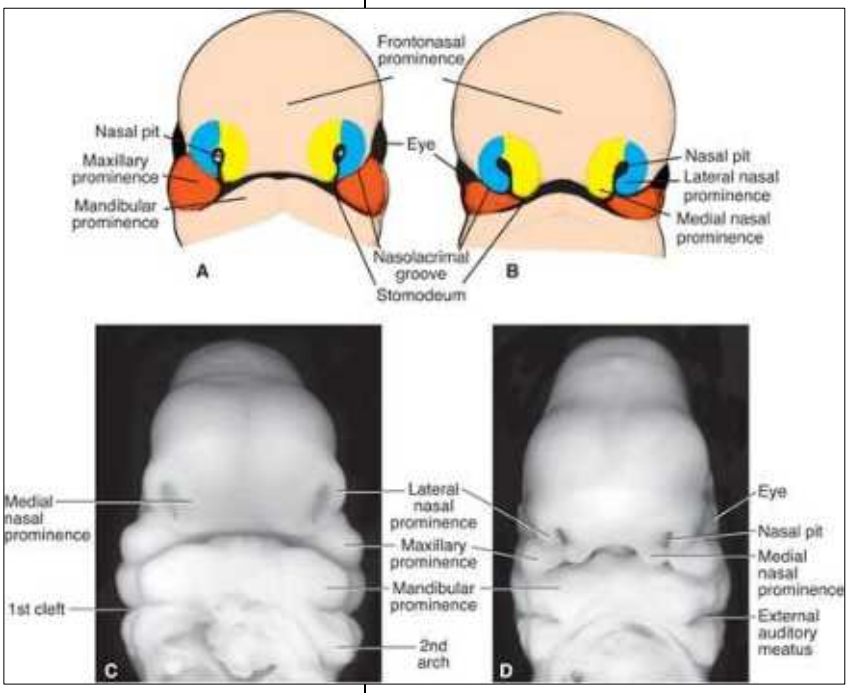
- **Unpaired frontonasal prominence**
- **Paired maxillary prominences**
- **Paired mandibular prominences**

Derivatives of the Frontonasal Prominence:

- **Nasal placodes** (ectodermal thickenings) → medial and lateral nasal prominences, nasal pit
- **Nasolacrimal groove**
- **Intermaxillary segment**
- **Nasal septum** (a deeper, midline structure)

Derivatives of the Intermaxillary Segment (formed by fusion of the medial nasal prominences):

- **Philtrum of the upper lip**
- **Fleshy nasal septum**
- **Premaxillary part of the maxilla** (hidden)
- **Primary palate** (hidden)

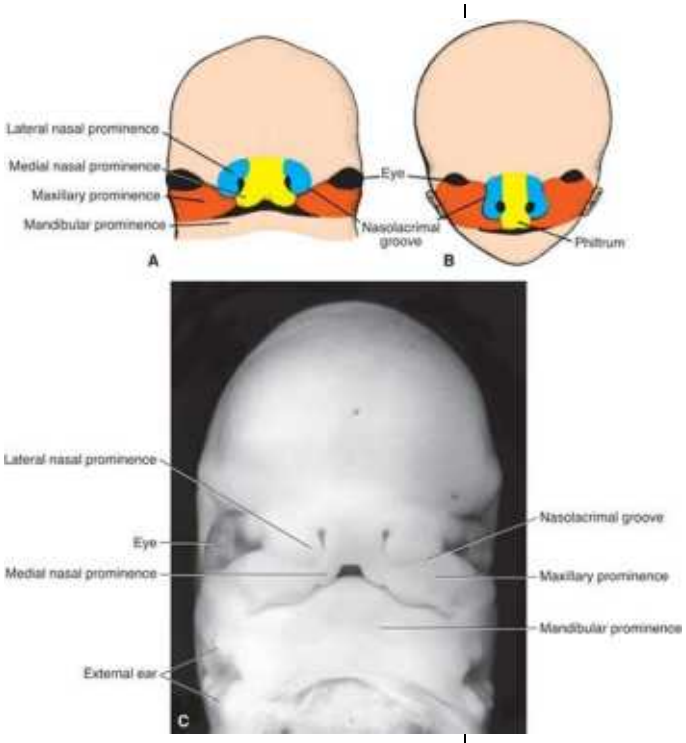


Note, all of the intermaxillary segment components are midline structures. **Retinoic acid** is a very important morphogen controlling the early development of the frontonasal prominence.

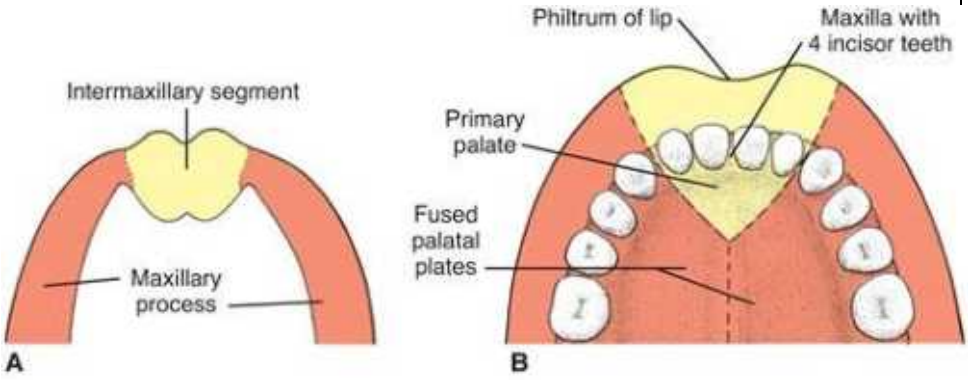
The **medial** and **lateral nasal prominences** develop due to **localized proliferation** of mesenchymal cells. Their elevations form the **nasal pit**, which marks the future site of the **external nasal opening**.

The **nasolacrimal groove** forms between the **lateral nasal prominence** and the **maxillary prominence** as both structures increase in size and robustness. Their expansion creates a distinct groove, which is eventually covered over to form the **nasolacrimal duct**, a key conduit for tear drainage from the eye to the nasal cavity.

Meanwhile, the **medial nasal prominences** proliferate more extensively than the lateral nasal prominences, allowing them to extend laterally and fuse with the medial aspect of the adjacent maxillary prominences. In the adult face, this fusion is reflected in the formation of the **philtrum**—the vertical groove in the upper lip located between two ridges. These ridges mark the sites where fusion occurred during development, and failure of this fusion can result in a **cleft lip**, typically occurring at one of these junctions.



The **mandibular prominences** enlarge and fuse at the midline during early facial development. Minor variations in this fusion process can result in the formation of a **chin dimple** in some individuals. Within the mandible, **Meckel's cartilage** develops and serves as a structural template around which the definitive lower jaw forms through **intramembranous ossification**. Abnormalities in this process are exceedingly rare.



It is important to emphasize that the **intermaxillary segment** (the central yellow region in the images) arises from the fusion of the **medial nasal prominences**. One key component of this segment is the upper jaw component (premaxilla) which houses the **four incisor teeth**.

The **primary palate** originates from mesenchymal condensations within the **median palatine processes**, located posterior to the incisor region (*see Figure above*). This portion of the premaxillary bone lies behind the bony area where the incisors are rooted.

The **primary palate** is positioned **anterior to** and is significantly **smaller than** the **secondary palate**, which forms from the fusion of the paired palatal shelves (*see image above*). Also derived from the intermaxillary segment is the **nasal septum**, which grows inferiorly toward the fusing nasal prominences and palatine processes (*see upcoming slides*).

The five facial primordia are the:

- unpaired **frontonasal prominence**
- paired **maxillary prominences**
- paired **mandibular prominences**.

The **frontonasal prominence**:

- most is from NCC
- nasal placodes (thickening of ectoderm)
- medial and lateral nasal prominences
- nasolacrimal groove
- intermaxillary segment
- nasal septum

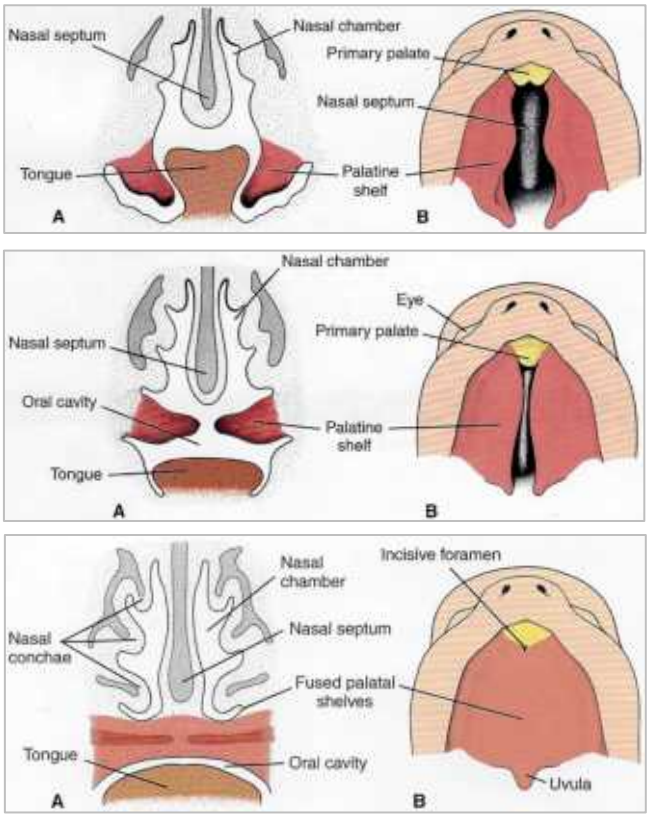
The **intermaxillary segment** (the central yellow region in the images):

- formed by fusion of the paired medial nasal processes

- labial component: philtrum of the lip, fleshy nasal septum
- upper jaw component with incisors (premaxilla)
- primary palate
- nasal septum

FORMATION OF THE PALATE

The **palate** develops from two distinct embryological components: an **unpaired median palatine process** and a **pair of lateral palatine processes** (also known as **palatal shelves**). The **median palatine process** arises as an outgrowth of the fused **medial nasal prominences**, forming part of the **intermaxillary segment**. This structure ultimately gives rise to the **primary palate**, which is often referred to as the **premaxillary part of the maxilla**. It is within this region that the **upper incisor teeth** will develop.



The **secondary palate** develops from the **lateral palatine shelves**, which are medial extensions of the **maxillary prominences**. Initially, the relatively large size of the **tongue** within the developing oral cavity prevents these shelves from approximating one another (*see figures above*). However, as development progresses, the lateral palatine shelves **elevate**, **rotate upward**, and **face each other**, allowing them to fuse and form the major portion of the secondary palate—also known as the **hard palate**.

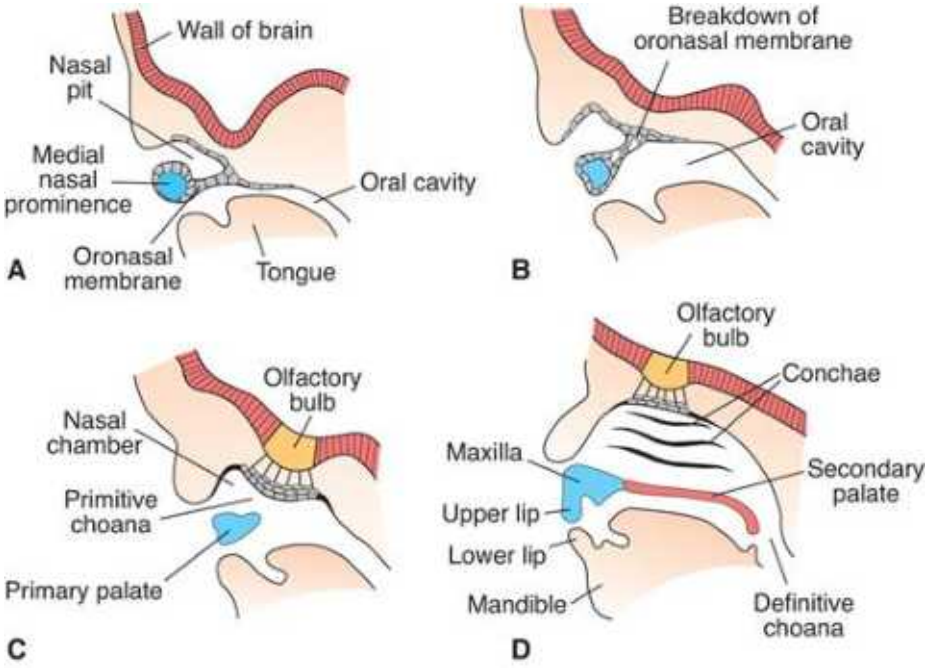
Bone formation occurs within the mesenchyme of the maxillary prominences through **intramembranous ossification**. Fusion of the lateral palatine shelves to form the secondary palate is typically completed by the **end of the 9th week** of gestation. These shelves also fuse with the **median palatine process** (which forms the **primary palate**). The **soft tissue components** of the lateral palatine shelves continue to fuse over the following two weeks, completing the formation of the **soft palate** by the **end of the 12th week**.

Additionally, **downgrowth of the nasal septum** from the **frontonasal prominence** contributes to the final formation of the secondary palate. The nasal septum fuses with both the **primary** and **secondary palates**, ensuring continuity between the oral and nasal cavities (*see figures above*).

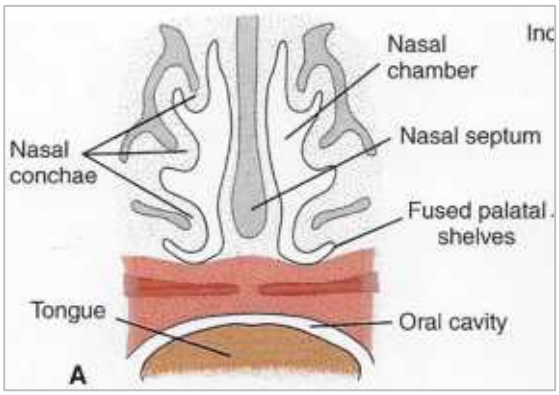
Primary palate:
- Also called premaxillary part of maxilla
- From outgrowth of median palatine process
- Fusion with lateral palatine shelves posteriorly
- Fuses with the nasal septum

Secondary palate:
- Fusion of lateral palatine shelves with each other and with nasal septum

FORMATION OF THE NOSE AND OLFACTORY APPARATUS



The formation of the **nose and olfactory apparatus** begins with the development of the **nasal placodes** within the **frontonasal prominence**. These placodes invaginate to form **nasal pits**, which are bordered by raised regions - the **medial nasal** and **lateral nasal prominences**. As the nasal pits deepen, they become separated from the oral cavity by the **oronasal membrane** (*see figure above*). Note that the sections shown in the figure are **para-sagittal**, meaning they lie adjacent to the midline.



Once the oronasal membrane breaks down, the **nasal** and **oral cavities** become continuous through the **nasal choanae**, located posterior and superior to the **primary palate**. An **epithelial plug** forms at the opening of the nasal pits and persists until the **fourth month**, after which it is removed via **apoptosis**.

Further development of the **nasal conchae** involves the formation of **diverticula** from the walls of the nasal cavity, which grow into adjacent developing bones and give rise to the **paranasal sinuses**.

The **nasal cavity** originates from the **invagination of superficial ectoderm**. Similarly, the **oral cavity lining** also arises from superficial ectoderm, referred to specifically as **oral ectoderm**. In contrast, **endoderm-derived epithelium** begins at the level of the **oropharynx**. This epithelial transition is mirrored in the **rectum**, where **endodermal epithelium** begins approximately **one-third of the way in**.

Nose and olfactory apparatus

- Frontonasal prominence
- Nasal placodes
- Medial nasal prominence
- Lateral nasal prominence
- Nasal pits
- Nasal septum
- Oronasal membrane must breakdown to allow communication between the nasal cavity and oral cavity

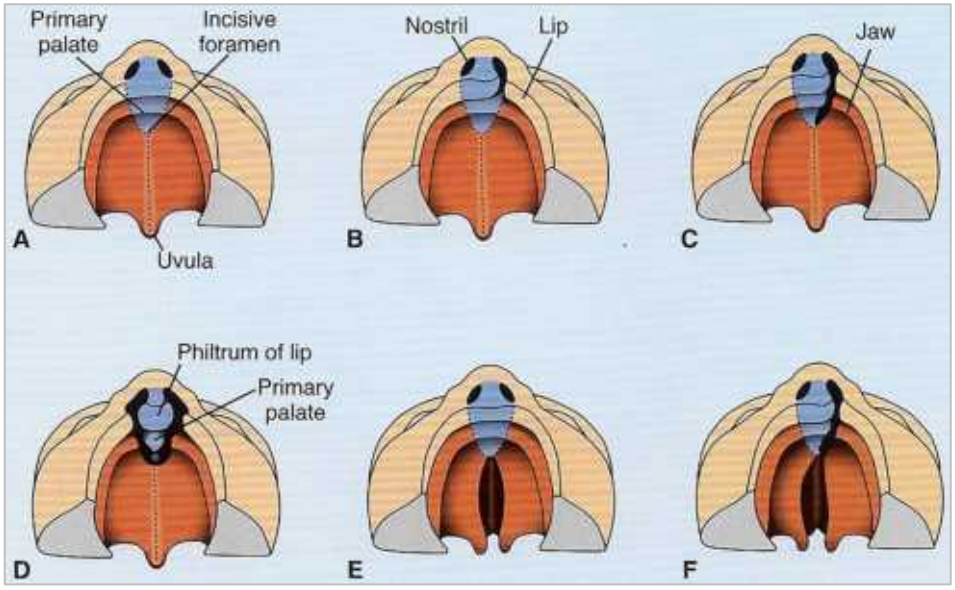
Superficial ectoderm (mucosa) lines:

- Nasal cavity
- Oral cavity (to oropharynx)

Developmental Timeline

- **Week 6–7**: Medial nasal + maxillary prominences fuse → upper lip
- **Week 9**: Lateral palatine shelves fuse → hard palate
- **Week 12**: Soft palate fusion completes
- **Month 4**: Epithelial plug at nasal pit removed by apoptosis

MALFORMATIONS OF THE CRANIOFACIAL REGION



Cleft Lip and Palate

🧬 Embryological Origins & Fusion Events

Structure	Derived From	Key Fusion Event
Upper Lip	Medial nasal + Maxillary prominences	Failure → **Cleft Lip**
Lower Lip	Mandibular prominences	Rare midline cleft
Primary Palate	Median palatine process (from medial nasal prominences)	Failure → **Anterior cleft palate**
Secondary Palate	Lateral palatine shelves (from maxillary prominences)	Failure → **Posterior cleft palate**
Nasal Septum	Frontonasal prominence	Must fuse with both palates

👶 Incidence & Sex Differences

Condition	Incidence	More Common In
Cleft Lip ± Palate	1 in 1,000 live births	**Males**
Cleft Palate ± Lip	1 in 2,500 live births	**Females**

Clinical Implications

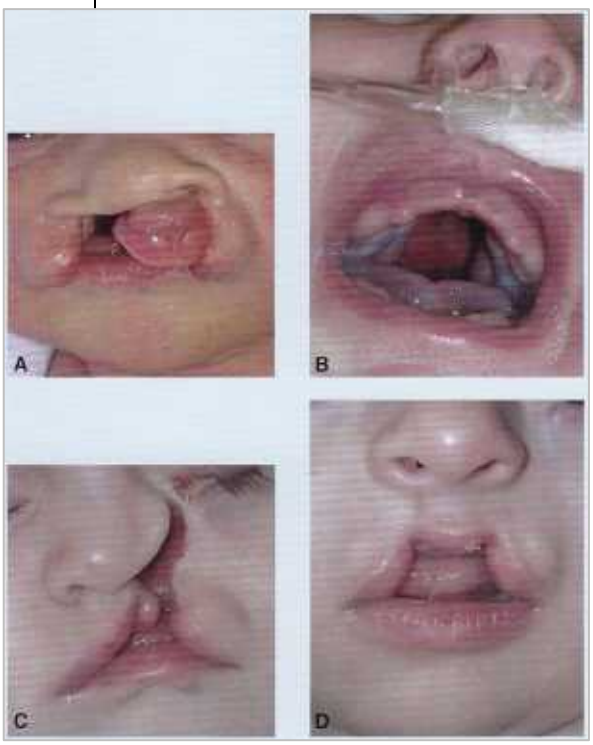
- Clefts may affect feeding, speech, and airway function
- Require surgical repair and multidisciplinary care
- Retinoic acid exposure is a known teratogen affecting facial development

SmileTrain www.smiletrain.org

Cleft lip:
Lack of fusion of
- **medial nasal prominences**
- **maxillary prominences**

Cleft palate:
Lack of fusion of
- **lateral palatine shelves**
- **nasal septum**

Other defects in this region include: *(see next page)*



Other defects in this region include:

- **Oblique facial cleft:** Results from a failure of fusion between the **lateral nasal** prominence and the **maxillary prominence**.
- **Macrostomia *(lateral facial cleft)*:** Caused by incomplete fusion between the **maxillary and mandibular prominences**, which can result in an abnormally large mouth on one side.
- **Median cleft lip:** Occurs due to incomplete merging of the **medial nasal prominences.**

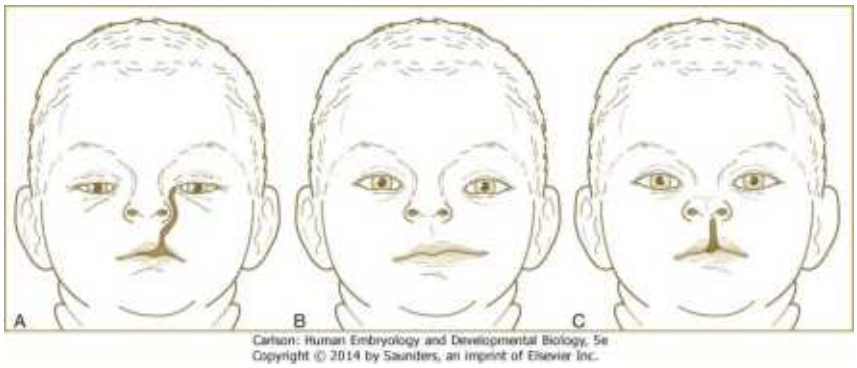


Figure 14.18. (A) Oblique facial cleft combined with a cleft lip. (B) Macrostomia on the left side. (C) Medial cleft lip with partial nasal cleft.

The figure below schematically illustrates these defects.

Oblique facial cleft
Defect in fusion of
- **lateral nasal prominence**
- **maxillary prominence**

Macrostomia (lateral facial cleft)
Defect in fusion of
- **maxillary prominences**
- **mandibular prominences**
- can result in a large mouth on one side.

Median cleft lip
Defect in fusion of
- medial nasal prominences

Frontal nasal dysplasia

Frontal nasal dysplasia encompasses a range of malformations resulting from **excessive tissue growth** or **abnormal development** within the **frontonasal prominence**.

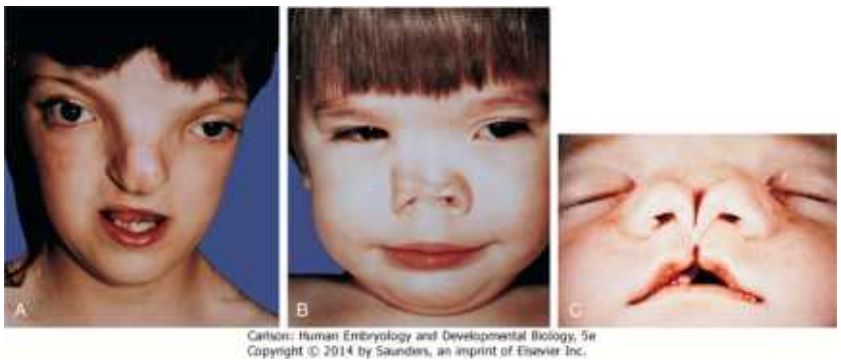


Figure 14.19. Varying degrees of frontal nasal dysplasia.

Three examples are shown in the figure above from Carlson (*Figure 14.19*). Note that both **oblique facial cleft** and **median cleft lip** are included in this category, as they involve the frontonasal prominence.

Frontal nasal dysplasia
Results from
- abnormal development of frontonasal prominence
- includes excessive tissue

DEVELOPMENT OF THE PHARYNX AND ITS DERIVATIVES

As previously mentioned, the **pharyngeal region** is defined by a series of **pharyngeal arches**, each separated externally by a **pharyngeal groove** and internally by a **pharyngeal pouch**. These arches give rise to distinct anatomical structures, as illustrated in *Figure 14.36* from Carlson.
In contrast to the rest of the embryo, where the **paraxial mesoderm** segments into discrete blocks known as **somites**, the **head region** retains a **continuous strand of mesoderm**. From this strand, mesodermal cells migrate into each developing pharyngeal arch to contribute to its structural components.
Although **six pharyngeal arches** form during development, the **fifth arch** is transient—it appears briefly and then regresses. Cells from the **sixth arch**, before it too disappears, migrate cranially and contribute to the formation of **laryngeal cartilages** (similarly to the 4th arch) and the **recurrent laryngeal nerve**.

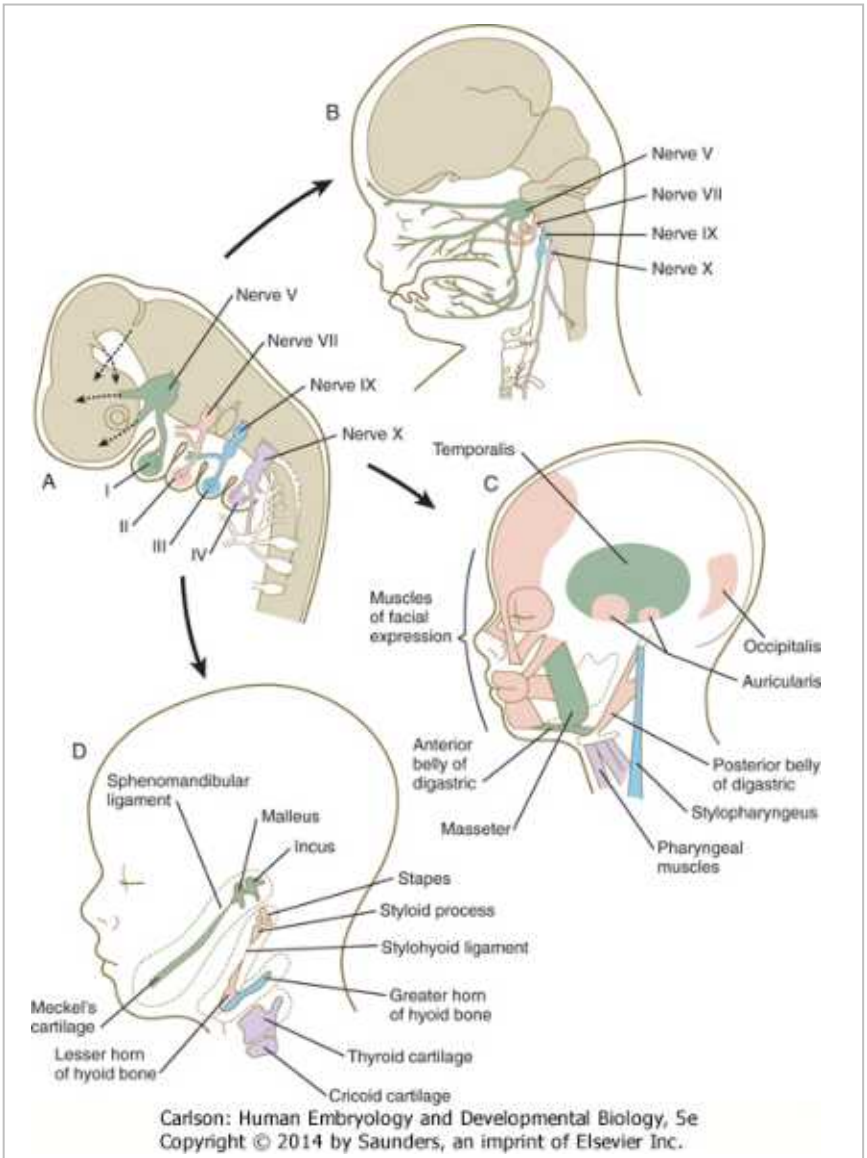


Figure 14.36. Pharyngeal arch showing adult derivatives of the neural, muscular and skeletal components of the arches.

Pharyngeal arch showing adult derivatives of the neural, muscular and skeletal components of the **arches color-coded for each of the four main arches**. A table is provided on the next page of these same relationships.

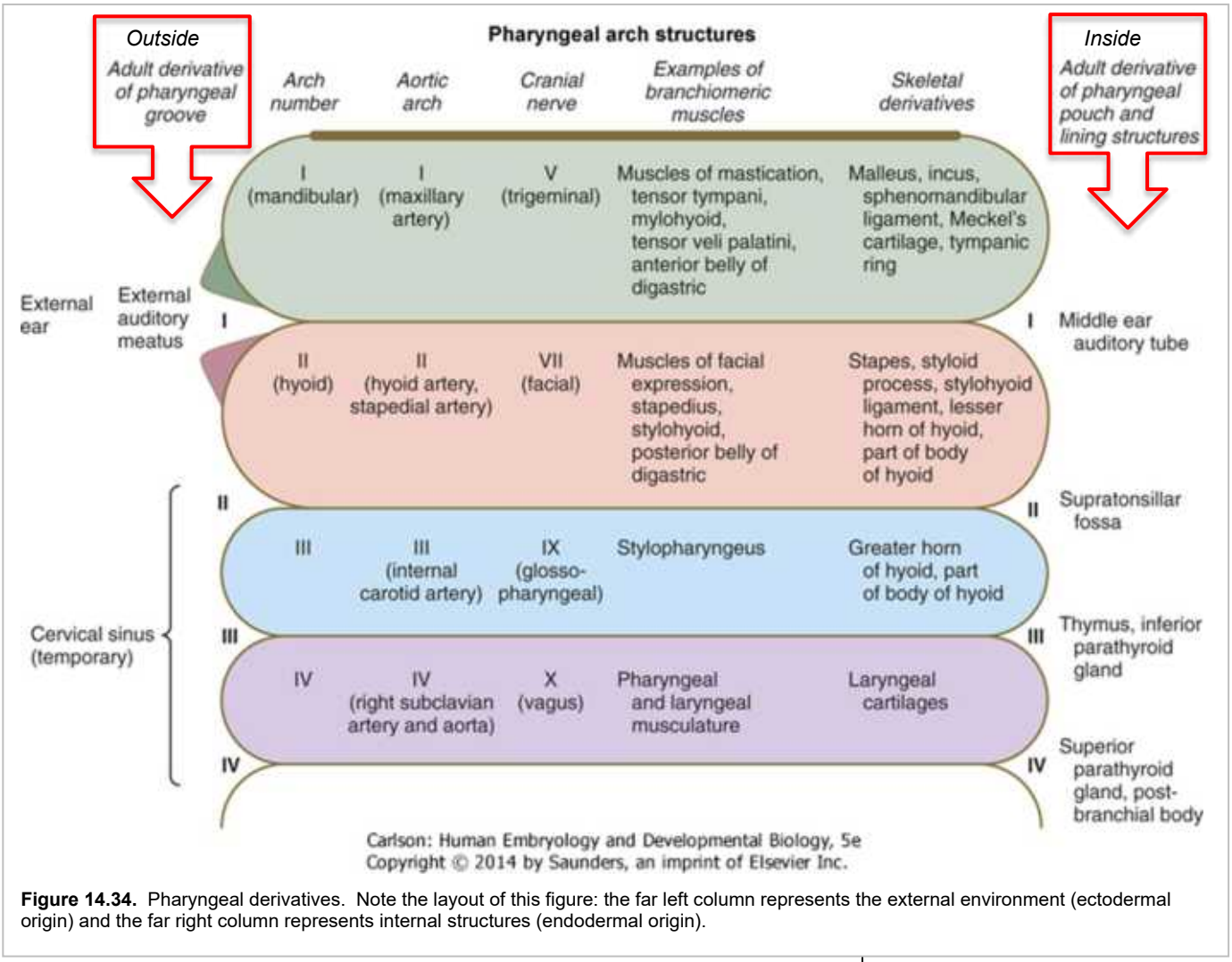


Figure 14.34. Pharyngeal derivatives. Note the layout of this figure: the far left column represents the external environment (ectodermal origin) and the far right column represents internal structures (endodermal origin).

Each **pharyngeal arch** contains an **artery** that passes through it. As discussed in the cardiovascular development lectures, each artery is associated with a specific arch (*see also Figure 14.34 above*). Notably, the **6th aortic arch** contributes to the formation of the **right and left pulmonary arteries**.

The schematic figure above—and the one on the previous page—provides a comprehensive summary of the **four primary pharyngeal arches**, detailing their associated **artery**, **cranial nerve**, **muscles**, and **skeletal components**. These figures also illustrate the developmental fates of the **ectodermally-derived grooves** and **endodermally-derived pouches**.

Understanding the relationships between the pharyngeal arches and their **innervation** and **vascular supply** is essential. As tissues migrate or become displaced from their original location within the pharyngeal arch system, they often retain their **original nerve supply**, which has important clinical implications.

You will be responsible for knowing the **artery**, **cranial nerve**, **muscle**, and **skeletal derivatives** associated with each pharyngeal arch. Mastery of these relationships is crucial for understanding conditions such as **first arch syndromes**. Be sure to refer to the figures above and on the previous page to reinforce these associations.

This **table** is actually a **figure** that illustrates the **derivatives of the four pharyngeal arches**, along with the **ectodermal derivatives** (shown in the far-left column) and **endodermal derivatives** (shown in the far-right column).

You will be responsible for knowing the specific **artery**, **cranial nerve**, **muscle**, and **skeletal components** associated with each arch.

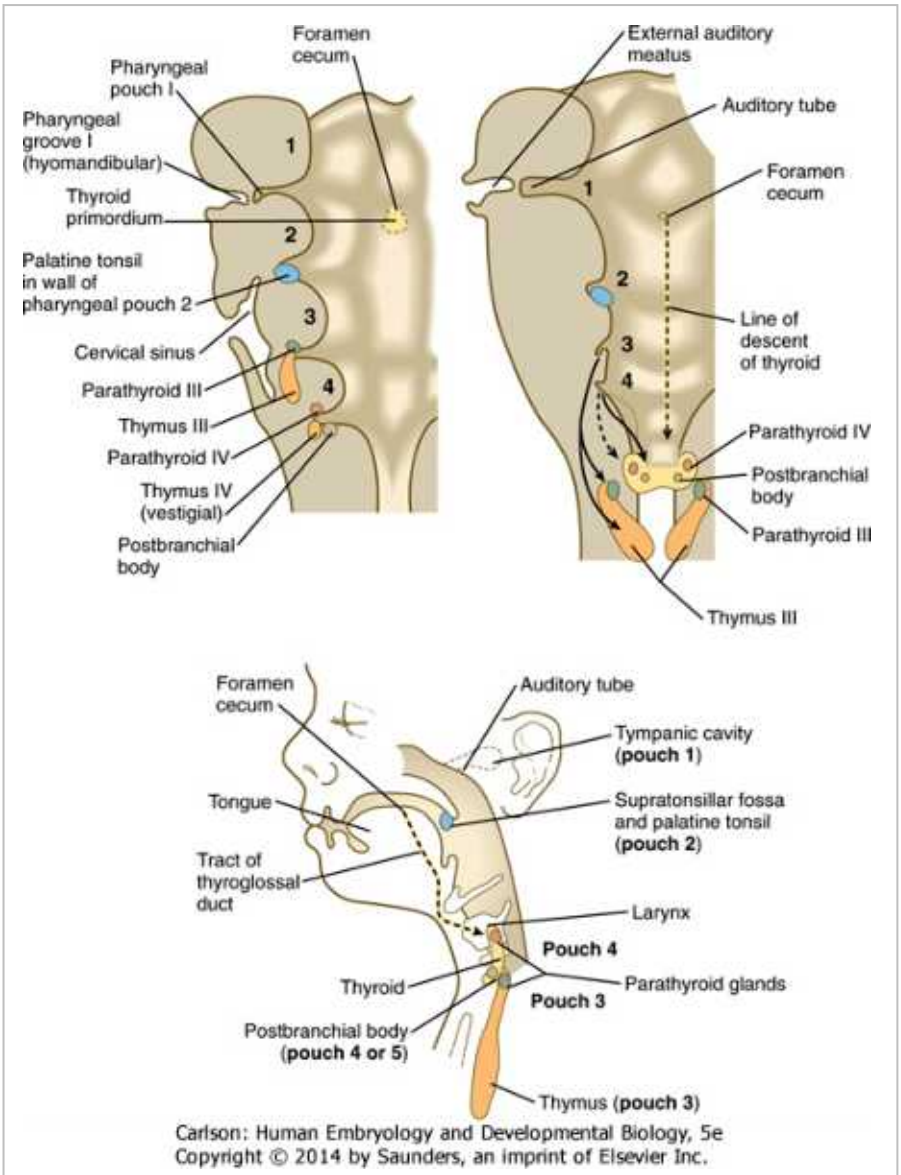


Figure 14.37. Embryonic origins and pathways of the primordia of glands derived from the pharyngeal pouches and the floor of the pharynx.

Of the **pharyngeal grooves** (ectodermal origin), only the **first pharyngeal groove** persists into adulthood, forming the **external auditory meatus**. Grooves **2 through 4** coalesce to form the **cervical sinus**, a transient structure that ultimately regresses and disappears (*see Figure 14.37*).

In contrast to the grooves, all of the **endodermally-derived pharyngeal pouches** give rise to distinct and permanent structures:

- The **first pharyngeal pouch** develops into the **tympanic cavity** and **auditory (Eustachian) tube**. The membrane formed by the adjacent ectoderm and endoderm becomes the **tympanic membrane**.
- The **second pouch** forms the **supratonsillar fossa**, and the surrounding lymphoid tissue differentiates into the **palatine tonsils**.
- The **third pharyngeal pouch** has dual fates:
    - Its **dorsal region** gives rise to the **inferior parathyroid glands**.
    - Its **ventral region** forms the **epithelial component of the thymus gland**.

GROOVES

Groove 1
- external auditory meatus

Grooves 2-4
- coalesce together and regress

POUCHES

Pouch 1
- tympanic cavity
- auditory tube

Pouch 2
- supratonsillar fossa
- palatine tonsils

Pouch 3
- dorsal region
    - **inferior parathyroid glands**
- ventral region
    - **thymus gland**

Pouch 4
- dorsal region
    - **superior parathyroid glands**
- ventral region
    - **ultimobranchial body**

These structures **migrate** from their initial locations in the **pharyngeal region** to more **caudal final destinations** during development. The **fourth pharyngeal pouch** contains both **dorsal** and **ventral components**, which differentiate and migrate independently.

- The **dorsal aspect** of the fourth pouch migrates and gives rise to the **superior parathyroid glands**.
- The **ventral aspect** primarily forms the **ultimobranchial body**, which becomes associated with the **thyroid gland**.

These regions are eventually **invested with neural crest cells**, which differentiate into **parafollicular cells (C cells)** - specialized endocrine cells that produce **calcitonin**, a hormone that lowers blood calcium levels.

Importantly, there is an **inverse relationship** between the **third** and **fourth pharyngeal pouches** in terms of their contributions to the **parathyroid glands**:

- The **third pouch** forms the **inferior parathyroid glands**.
- The **fourth pouch** forms the **superior parathyroid glands**.

The **thyroid gland** is a **midline structure** derived from **pharyngeal endoderm** located between the **first and second pharyngeal pouches**. Its development begins with the formation of the **thyroid diverticulum**, an outpouching that marks the initial stage of thyroid morphogenesis.

As the gland matures, it **descends** from its origin to its final position in the **anterior neck**, leaving behind a small depression at the base of the tongue known as the **foramen cecum**. During this descent, the thyroid remains connected to its origin via the **thyroglossal duct**, a transient midline structure that typically regresses. Remnants of this duct may persist and can give rise to **thyroglossal duct cysts**, which are clinically significant midline neck masses.

Stage	Feature	Details
Origin	Pharyngeal endoderm	Located between **1st and 2nd pharyngeal pouches**
Initial Structure	Thyroid diverticulum	Midline outpouching from the floor of the primitive pharynx
Migration Path	Descends into neck	Leaves behind the **foramen cecum** at the base of the tongue
Transient Structure	Thyroglossal duct	Midline tract connecting origin to final position; usually regresses
Final Position	Anterior neck	Lies anterior to trachea, below thyroid cartilage
Associated Cells	Neural crest-derived C cells	Incorporated via **ultimobranchial body**; secrete **calcitonin**
Clinical Note	Thyroglossal duct cyst	Midline neck mass due to persistent duct remnants

Thyroid gland

- midline structure
- diverticulum of endoderm
- descends to final position
- leaves **foramen cecum** in tongue

The **pituitary gland** (hypophysis) originates from **two** distinct **ectodermal** sources: the floor of the **diencephalon** and **Rathke's pouch**, an invagination of the oral ectoderm at the roof of the pharynx near the stomodeum. Although this region lies within the oropharyngeal cavity, it's important to note that its lining is derived from ectodermal tissue.

As illustrated in Carlson (Figure 14.38), these two components interact during embryogenesis to form the **anterior and posterior lobes** of the pituitary gland. Over time, the stalk of Rathke's pouch regresses, leaving behind the anterior lobe, which differentiates into the **anterior pituitary** (pars distalis). Meanwhile, the **neural component** gives rise to the **posterior pituitary** (pars nervosa).

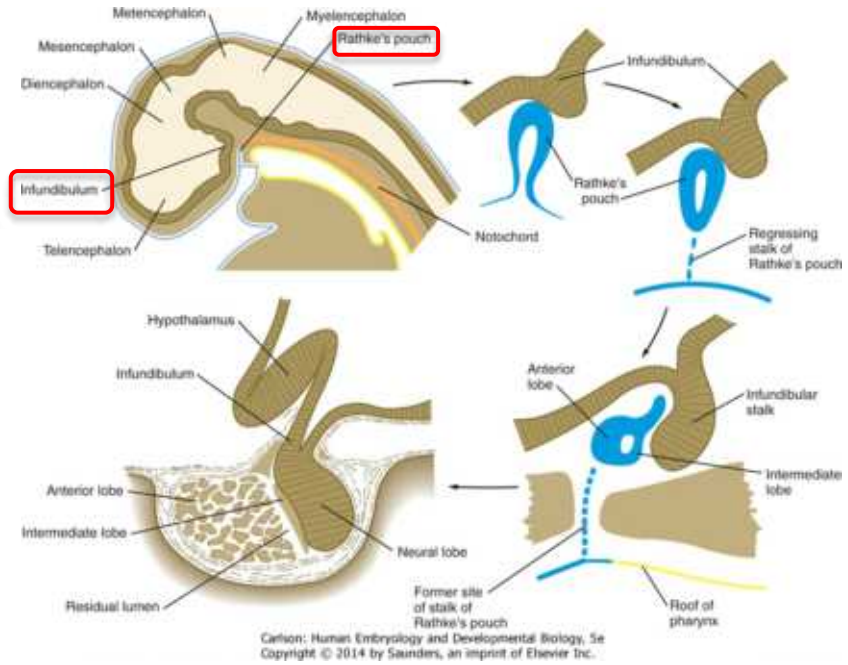


Figure 14.38. Development of the pituitary gland (hypophysis).

Pituitary gland

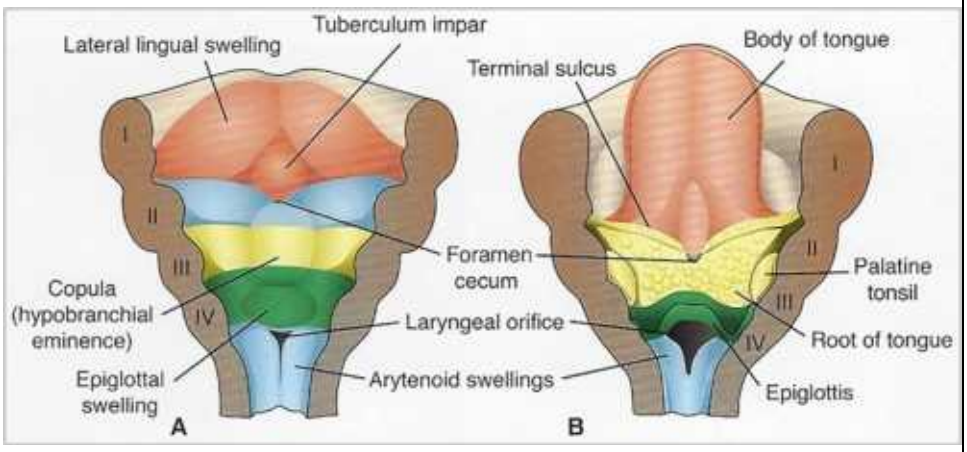
- **Ectodermal tissue**
- **Posterior pituitary**
  - a.k.a. *pars nervosa*
  - floor of diencephalon
- **Anterior pituitary**
  - a.k.a *pars distalis*
  - roof of pharynx (Rathke's pouch)

FORMATION OF THE TONGUE

The tongue originates from four mesenchymal swellings in the floor of the embryonic pharynx (see Figure below)

- **Lateral lingual swellings** (paired) - derived from the first pharyngeal arch
- **Tuberculum impar** - positioned between the first and second arches
- **Copula (hypobranchial eminence)** - primarily associated with the third arch

During development, the lateral lingual swellings enlarge and merge to form the anterior two-thirds of the tongue. Although the tuberculum impar appears early, it contributes minimally to the mature structure. The copula, along with contributions from the fourth arch, overgrows the second arch, which ultimately plays no structural role in tongue formation—its only legacy is the innervation by cranial nerve VII.



This pattern of arch contribution is crucial for understanding tongue innervation:

- **Anterior tongue mucosa** (anterior two-thirds) arises from **first arch ectoderm**
- **Posterior tongue mucosa** (posterior one-third) derives from **third and fourth arch endoderm**
- **Intrinsic tongue muscles** originate from **occipital somite myotomes** (mesoderm), not pharyngeal arches

Key Point: The first, third, and fourth arches are the primary contributors to tongue development. The second arch is not structurally represented, despite its associated nerve.

Tongue Anomalies

- **Macroglossia** — abnormally large tongue
- **Microglossia** — abnormally small tongue
- **Ankyloglossia (tongue-tie)** — restricted tongue movement due to incomplete regression of the frenulum during development

Macroglossia Microglossia Ankyloglossia

Tongue derivatives:

- **Arch 1**
  - **Lateral lingual swellings**
  - **Tuberculum impar**
  - **CN V** (GSA, ant. 2/3, V_3)
- **Arch 2**
  - No structural contribution
  - **CN VII** (SA, taste ant. 2/3)
- **Arch 3**
  - **Copula** (hypobranchial eminence)
  - **CN IX** (GSA; SA, taste post. 1/3)
- **Arch 4**
  - Extreme posterior part
  - Epiglottis
  - **CN X** (GSA; SA, taste post. Epiglottic cart.)

Tongue muscle:

- Mesoderm from occipital somite myoblasts
- **CN XII** all muscles except for palatoglossus
- **CN X** palatoglossus

Anomalies of the tongue:

- **Macroglossia** (large)
- **Microglossia** (small)
- **Ankyloglossia** (tongue-tie, frenulum)

MALFORMATIONS OF THE PHARYNX AND ITS DERIVATIVES

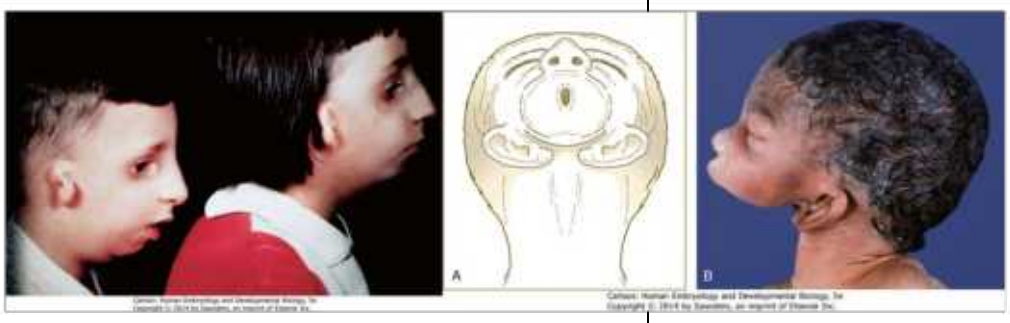
First Arch Syndromes

Maldevelopment of the first pharyngeal arch can lead to several congenital syndromes.
One notable example is **Pierre Robin Syndrome**, also referred to as **Pierre Robin Sequence**. This condition is characterized by **severe micrognathia** (an underdeveloped mandible), **cleft palate**, and **ear anomalies**.
The term "sequence" reflects the cascading nature of developmental events: the initial mandibular hypoplasia displaces the tongue posteriorly into the pharynx (glossoptosis), which interferes with palatal closure, resulting in a cleft palate. The posterior tongue position may also contribute to **airway obstruction**, complicating breathing in affected infants.

Figure from: http://www.myhealthyfeeling.com/pierre-robin-syndrome-pictures-symptoms-treatment-causes/. This figure shows Pierre Robin Syndrome in three separate individuals.

Recurrent **ear infections** are commonly observed, although the precise link between mandibular deficiency, tongue displacement, and middle ear dysfunction remains unclear. These features underscore the interconnectedness of craniofacial development and the importance of first arch integrity.

Another example is the **Treacher Collins Syndrome** (Mandibulofacial Dysostosis). Treacher Collins Syndrome is a craniofacial disorder caused by abnormal development of the first pharyngeal arch. It shares features with Pierre Robin Sequence, such as **mandibular hypoplasia** and **cleft palate**, but includes additional defects.
These include **zygomatic bone underdevelopment**, **external ear malformations** (e.g., microtia), and **lower eyelid colobomas**. Unlike Pierre Robin, ear issues are structural rather than infectious. In severe cases, **agnathia**—complete absence of the lower jaw—may occur, leading to significant airway and feeding challenges.



Figures 14.42 and 14.43. Examples of Treacher Collins syndrome.

First Arch Syndromes

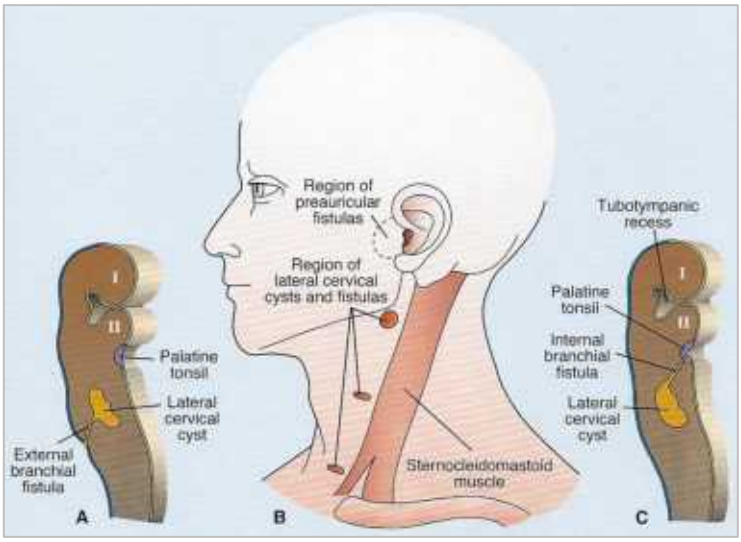
Pierre Robin Syndrome (Sequence)
- Micrognathia
- Cleft palate
- Ear defects

Treacher Collins Syndrome (more extensive than Pierre Robin Syndrome)
- Micrognathia
- Cleft palate
- Ear defects
- Zygomatic bone defects
- Eye defects

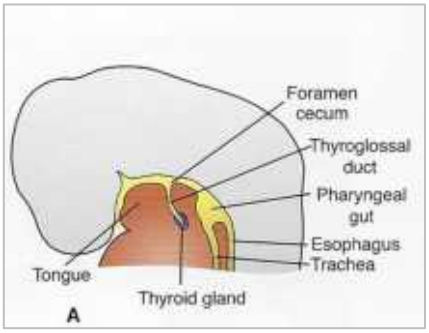
Jono Lancaster

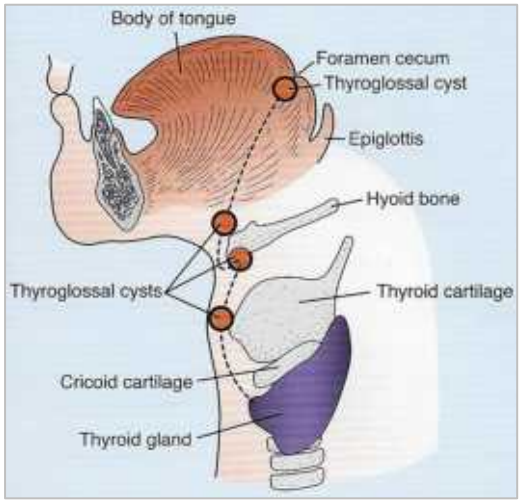
https://www.samebutdifferentcic.org.uk/we-will-not-hide-jono

Lateral Cysts, Sinuses and Fistulas: Persistent Pharyngeal Grooves



These anomalies result from the persistence or abnormal regression of **pharyngeal grooves**, particularly the **cervical sinus**. They typically appear **lateral to the neck**, adjacent to the **sternocleidomastoid muscle**, and may present as a **cyst**, **sinus**, or **fistula**, depending on severity.





Thyroglossal Duct Remnants

Ectopic thyroid tissue can occur anywhere along the **midline path** of thyroid primordium migration. These midline lesions are easily distinguished from lateral cervical sinus remnants. Before surgical removal, it's essential to confirm whether the ectopic tissue constitutes the **entire thyroid gland**, as shown in the common sites illustrated above.

Figure 14.46. Individual with thyroglossal duct sinus.

Lateral Cysts, Sinuses and Fistulas

- Abnormal cervical sinus regression
- Lateral anomaly
- Anterior to SCM muscle

Thyroglossal Duct Remnants

- Persistent thyroid tissue along pathway of descent of thyroid
- Midline anomaly

Ectopic Parathyroid and Thymic Tissue: Pharyngeal Pouches

Due to their extensive migration during early embryogenesis, parathyroid glands and thymic tissue can occasionally be found in ectopic locations. These displacements are usually asymptomatic, but—similar to ectopic thyroid tissue—recognizing their presence is crucial during surgical procedures.

Common sites for ectopic parathyroid and thymic tissue are illustrated in Figure 14.48. **Surgeons must consider these possibilities to avoid misidentifying or inadvertently removing functional tissue.**

Ectopic Parathyroid or Thymic Tissue
- Ectopic tissue along pathway of descent

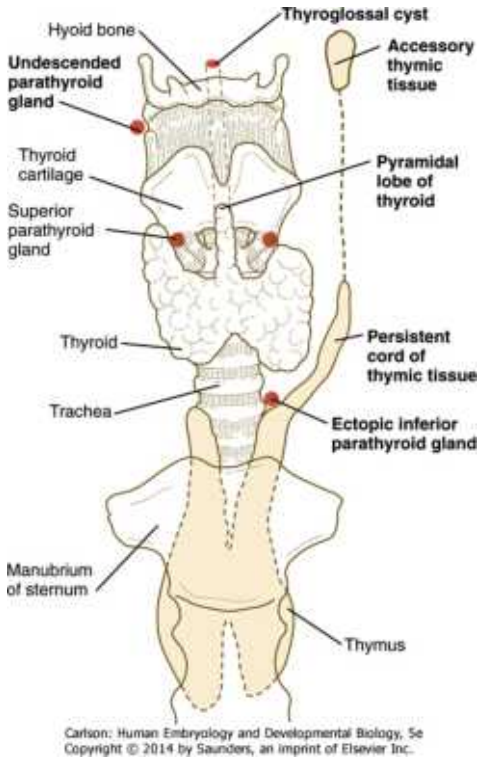


Figure 14.48. Locations where abnormally positioned pharyngeal glands or portions of glands can be found.

Figure 17.16BC from Langman's *Medical Embryology*, © 2015, 13e.

DiGeorge's Syndrome

DiGeorge Syndrome (22q11.2 Deletion Syndrome / Velo-Cardio-Facial Syndrome)

DiGeorge Syndrome results from a deficiency in **cranial neural crest cells**, leading to impaired development of the **third and fourth pharyngeal pouches**. This disrupts formation of the **thymus** and **parathyroid glands**, causing **immunodeficiency** and **hypoparathyroidism**.

Common features include:

- **Cleft palate**
- **Micrognathia**
- **Small mouth**
- **Smooth philtrum**
- **Prominent nasal bridge**
- **Posteriorly rotated ears**

Cardiac anomalies, especially **persistent truncus arteriosus (PTA)**, stem from disrupted neural crest migration affecting the heart's outflow tract. Mutations in the **Tbx1 gene** have been linked to DiGeorge-like presentations.

DiGeorge Syndrome (22q11.2 deletion)
- Failure of 3rd and 4th pouch development.
- Features:
- Hypoplastic thymus → T-cell immunodeficiency.
- Hypocalcemia due to absent parathyroids.
- Cardiac outflow tract defects (e.g., Tetralogy of Fallot).
- Facial dysmorphism: low-set ears, small jaw.

CHARGE Syndrome

CHARGE Syndrome is a complex genetic condition caused most often by mutations in the **CHD7 gene**, affecting neural crest cell development. The name is an acronym representing its key features:

- **C**: *Coloboma* of the eye
- **H**: *Heart defects* (commonly conotruncal anomalies)
- **A**: *Atresia of the choanae* (blockage of nasal passages)
- **R**: *Retardation of growth and development*
- **G**: *Genital anomalies*
- **E**: *Ear abnormalities* (including hearing loss and malformed external ears)

These features reflect disruptions in multiple embryonic structures, many of which are neural crest-derived. Severity and presentation vary widely, and early diagnosis is crucial for coordinated care.

Comparison chart highlighting the key differences and similarities between **DiGeorge Syndrome** and **CHARGE Syndrome**:

Feature	DiGeorge Syndrome	CHARGE Syndrome
Genetic Cause	22q11.2 deletion (Tbx1 gene implicated)	CHD7 gene mutation
Embryologic Basis	Cranial neural crest cell deficiency affecting 3rd & 4th pharyngeal pouches	Neural crest cell dysfunction affecting multiple systems
Immune System	Thymic hypoplasia → T-cell immunodeficiency	May have immune issues, but not a defining feature
Endocrine	Hypoparathyroidism due to parathyroid gland defects	Possible hormonal issues, but not central
Facial Features	Micrognathia, small mouth, smooth philtrum, prominent nasal bridge, posteriorly rotated ears	Coloboma, facial asymmetry, ear anomalies
Palate	Cleft palate	Cleft palate
Cardiac Defects	Conotruncal anomalies (e.g., persistent truncus arteriosus)	Conotruncal anomalies (e.g., tetralogy of Fallot, ASD, VSD)
Eye Defects	Not typical	Coloboma of iris or retina
Ear Defects	Posteriorly rotated ears	External ear malformations, hearing loss
Growth & Development	Developmental delays may occur	Growth retardation and developmental delay common
Other Names	Velo-cardio-facial syndrome	—

CHARGE syndrome

Coloboma

Heart defects
Atresia of the choanae
Retardation (growth, development)
Genital anomalies
Ear anomalies

Summary tables

Germ Layer Contributions

Germ Layer	Structures Formed
Ectoderm	Skin, oral cavity epithelium, neural tissue, sensory placodes
Mesoderm	Muscles of mastication and facial expression, vasculature
Endoderm	Pharyngeal lining, glands (thyroid, parathyroid)
Neural Crest	Craniofacial bones/cartilage, sensory ganglia, connective tissue

Derivatives of Pharyngeal Arches

Pharyngeal Arch	Skeletal Derivatives	Muscular Derivatives	Nerve Supply	Arterial Supply
1st Arch	Maxilla, mandible, malleus, incus, Meckel's cartilage	Muscles of mastication, mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini	CN V3 (mandibular branch of trigeminal)	Maxillary artery
2nd Arch	Stapes, styloid process, lesser horn of hyoid, stylohyoid ligament	Muscles of facial expression, stapedius, stylohyoid, posterior belly of digastric	CN VII (facial nerve)	Stapedial artery (regresses)
3rd Arch	Greater horn and lower body of hyoid	Stylopharyngeus	CN IX (glossopharyngeal nerve)	Common and internal carotid arteries
4th Arch	Laryngeal cartilages (thyroid, cricoid, arytenoid, etc.)	Pharyngeal constrictors, cricothyroid, levator veli palatini	CN X (superior laryngeal branch of vagus)	Arch of aorta (left), right subclavian artery
6th Arch	Laryngeal cartilages (shared with 4th arch)	Intrinsic muscles of larynx (except cricothyroid)	CN X (recurrent laryngeal branch of vagus)	Pulmonary arteries

Pharyngeal Pouches (Endoderm)

Pouch	Derivatives
1st	Middle ear cavity, auditory tube
2nd	Palatine tonsils
3rd	Thymus, inferior parathyroids
4th	Superior parathyroids
5th	Ultimobranchial body (C cells of thyroid)

Pharyngeal Grooves (Ectoderm)

- Only the **1st groove** persists → external auditory meatus
- Others are obliterated

Pharyngeal Membranes

- Only the **1st membrane** persists → tympanic membrane

(Tables by Co-Plot)