Head and Neck

Mesenchyme for formation of the head region is derived from **paraxial** and **lateral plate mesoderm, neural crest**, and thickened regions of ectoderm known as **ectodermal placodes**. Paraxial mesoderm (**somites** and **somitomeres**) forms a large portion of the membranous and cartilaginous components of the neurocranium(skull), all voluntary muscles of the craniofacial region, the dermis and connective tissues in the dorsal region of the head, and the meninges caudal to the prosencephalon. Lateral plate mesoderm forms the laryngeal cartilages (arytenoid and cricoid) and connective tissue in this region. Neural crest cells originate in the neuroectoderm of forebrain, midbrain, and hindbrain regions and migrate ventrally into the pharyngeal arches and rostrally around the forebrain and optic cup into the facial region. In these locations, they form the entire viscerocranium (face) and parts of the membranous and cartilaginous regions of the neurocranium (skull). They also form all other tissues in these regions, including cartilage, bone, dentin, tendon, dermis, pia and arachnoid, sensory neurons, and glandular connective tissue. Cells from **ectodermal placodes**, together with neural crest, form neurons of the fifth, seventh, ninth, and tenth cranial sensory ganglia. The most distinctive feature in development of the head and neck is the presence of **pharyngeal arches** (the old term for these structures is **branchial arches** because they somewhat resemble the gills [branchia] of a fish). These arches appear in the fourth and fifth weeks of development and contribute to the characteristic external appearance of the embryo. Initially, they consist of bars of mesenchymal tissue separated by deep clefts known as **pharyngeal clefts**. Simultaneously, with development of the arches and clefts, a number of outpocketings, the **pharyngeal pouches**, appear along the lateral walls of the pharynx, the most cranial part of the foregut. The pouches penetrate the surrounding mesenchyme, but do not establish an open communication with the external clefts. Hence, although development of pharyngeal arches, clefts, and pouches resembles formation of gills in fishes and amphibians, in the human embryo, real gills are never formed. Therefore, the term **pharyngeal** (arches, clefts, and pouches) has been adopted for the human embryo. Pharyngeal arches not only contribute to formation of the neck, but also play an important role in formation of the face. At the end of the fourth week, the center of the face is formed by the stomodeum, surrounded by the first pair of pharyngeal arches. When the embryo is 42 days old, five mesenchymal prominences can be recognized: the **mandibular prominences** (first pharyngeal arch), caudal to the stomodeum; the **maxillary prominences** (dorsal portion of the first pharyngeal arch), lateral to the stomodeum; and the **frontonasal prominence**, a slightly rounded elevation cranial to the stomodeum. Development of the face is later complemented by formation of the **nasal prominences**. In all cases, differentiation of structures derived from arches, pouches, clefts, and prominences is dependent on epithelial–mesenchymal interactions.

PHARYNGEAL ARCHES

Each pharyngeal arch consists of a core of mesenchymal tissue covered on the outside by surface ectoderm and on the inside by epithelium of endodermal origin. In addition to mesenchyme derived from paraxial and lateral plate mesoderm, the core of each arch receives substantial numbers of **neural crest cells**, which migrate into the arches to contribute to **skeletal components** of the face. The original mesoderm of the arches gives rise to the musculature of the face and neck. Thus, each pharyngeal arch is characterized by its own **muscular components**. The muscular components of each arch have their own **cranial nerve**, and wherever the muscle cells migrate, they carry their **nerve component** with them. In addition, each arch has its own **arterial component**.

First Pharyngeal Arch The **first pharyngeal arch** consists of a dorsal portion, the **maxillary process**, which extends forward beneath the region of the eye, and a ventral portion, the **mandibular process**, which contains **Meckel's cartilage**. During further development, Meckel's cartilage disappears except for two small portions at its dorsal end that persist and form the **incus** and **malleus**. Mesenchyme of the maxillary process gives rise to the **premaxilla, maxilla, zygomatic bone**, and part of the **temporal bone** through membranous ossification. The **mandible** is also formed by membranous ossification of mesenchymal tissue surrounding Meckel's cartilage. In addition, the first arch contributes to formation of the bones of the middle ear. Musculature of the first pharyngeal arch includes the **muscles of mastication** (temporalis, masseter, and pterygoids), **anterior belly of the digastric, mylohyoid, tensor tympani**, and **tensor palatini**. The **nerve** supply to the muscles of the first arch is provided by the **mandibular branch of the trigeminal nerve**. Since mesenchyme from the first arch also contributes to the dermis of the face, sensory supply to the skin of the face is provided by **ophthalmic, trigeminal nerve**. Muscles of the arches do not always attach to the bony or cartilaginous components of their own arch but sometimes migrate into surrounding regions. Nevertheless, the origin of these muscles can always be traced, since their nerve supply is derived from the arch of origin.

Second Pharyngeal Arch The cartilage of the **second** or **hyoid arch (Reichert's cartilage)** gives rise to the **stapes, styloid process of the temporal bone, stylohyoid ligament**, and ventrally, the **lesser horn** and **upper part of the body of the hyoid bone**. Muscles of the hyoid arch are the **stapedius, stylohyoid, posterior belly of the digastric, auricular, and muscles of facial expression**. The **facial nerve**, the nerve of the second arch, supplies all of these muscles.

Third Pharyngeal Arch The **cartilage** of the third pharyngeal arch produces the **lower part of the body** and **greater horn of the hyoid bone**. The **musculature** is limited to the

stylopharyngeus muscles. These muscles are innervated by the **glossopharyngeal nerve**, the nerve of the third arch.

Fourth and Sixth Pharyngeal Arches **Cartilaginous components** of the fourth and sixth pharyngeal arches fuse to form the **thyroid**, cricoid, arytenoid, corniculate, and cuneiform cartilages of the **larynx**. **Muscles** of the fourth arch (**cricothyroid, levator palatini**, and **constrictors of the pharynx**) are innervated by the **superior laryngeal branch of the vagus**, the nerve of the fourth arch. Intrinsic muscles of the larynx are supplied by the **recurrent laryngeal branch of the vagus**, the nerve of the sixth arch.

PHARYNGEAL POUCHES

The human embryo has four pairs of pharyngeal pouches; the fifth is rudimentary. Since the **epithelial endodermal lining** of the pouches gives rise to a number of important organs, the fate of each pouch is discussed separately.

First Pharyngeal Pouch The first pharyngeal pouch forms a stalk-like diverticulum, the **tubotympanic recess**, which comes in contact with the epithelial lining of the first pharyngeal cleft, the future **external auditory meatus**. The distal portion of the diverticulum widens into a sac-like structure, the **primitive tympanic** or **middle ear cavity**, and the proximal part remains narrow, forming the **auditory (eustachian) tube**. The lining of the tympanic cavity later aids in formation of the **tympanic membrane** or **eardrum**.

Second Pharyngeal Pouch The epithelial lining of the second pharyngeal pouch proliferates and forms buds that penetrate into the surrounding mesenchyme. The buds are secondarily invaded by mesodermal tissue, forming the primordium of the **palatine tonsils**. During the third and fi fth months, the tonsil is infiltrated by lymphatic tissue. Part of the pouch remains and is found in the adult as the **tonsillar fossa**.

Third Pharyngeal Pouch The third and fourth pouches are characterized at their distal extremity by a dorsal and a ventral wing. In the fifth week, epithelium of the dorsal region of the third pouch differentiates into the **inferior parathyroid gland**, while the ventral region forms the **thymus**. Both gland primordia lose their connection with the pharyngeal wall, and the thymus then migrates in a caudal and a medial direction, pulling the **inferior parathyroid** with it. Although the main portion of the thymus moves rapidly to its final position in the anterior part of the thorax, where it fuses with its counterpart from the oppositeside, its tail portion sometimes persists eitherembedded in the thyroid gland or as isolated thymic nests. Growth and development of the thymus continue until puberty. In the young child, the thymus occupies considerable space in the thorax and lies behind the sternum and anterior to the pericardium and great vessels. In older persons, it is difficult to recognize, since it is atrophied and replaced by fatty tissue. The parathyroid tissue of the third pouch finally comes to rest on the dorsal surface of the thyroid gland and forms the **inferior parathyroidgland**.

Fourth Pharyngeal Pouch Epithelium of the dorsal region of the fourth pharyngeal pouch forms the **superior parathyroid gland**. When the parathyroid gland loses contact with the wall of the pharynx, it attaches itself to the dorsal surface of the caudally migrating thyroid as the **superior parathyroid gland**. The ventral region of the fourth pouch gives rise to the **ultimobranchial body**, which is later incorporated into the thyroid gland. Cells of the ultimobranchial body give rise to the **parafollicular**, or **C, cells** of the thyroid gland. These cells secrete **calcitonin**, a hormone involved in regulation of the calcium level in the blood.

PHARYNGEAL CLEFTS

The 5-week embryo is characterized by the presence of four pharyngeal clefts, of which only one contributes to the definitive structure of the embryo.

The dorsal part of the first cleft penetrates the underlying mesenchyme and gives rise to the **external auditory meatus**. The epithelial lining at the bottom of the meatus participates in formation of the **eardrum**. Active proliferation of mesenchymal tissue in the second arch causes it to overlap the third and fourth arches. Finally, it merges with the **epicardial ridge** in the lower part of the neck, and the ***second, third, and fourth clefts*** lose contact with the outside. The clefts form a cavity lined with ectodermal epithelium, the **cervical sinus**, but with further development, this sinus disappears.

Pharyngeal Arch	**Nerve**	**Muscles**	**Skeleton**
1. Mandibular (maxillary and mandibular processes)	V. Trigeminal: maxillary and mandibular divisions	Mastication (temporal; masseter, medial, lateral pterygoids); mylohyoid, anterior belly of digastric, tensor palatine, tensor tympani	Premaxilla, maxilla, zygomatic bone, part of temporal bone, Meckel's cartilage, mandible malleus, incus, anterior ligament of malleus, sphenomandibular ligament
2. Hyoid	VII Facial	Facial expression (buccinator, auricularis, frontalis, platysma, orbicularis oris, orbicularis oculi) posterior belly of digastric, stylohyoid, stapedius	Stapes, styloid process, stylohyoid ligament, lesser horn and upper portion of body of hyoid bone
3.	IX. Glossopharyngeal	Stylopharyngeus	Greater horn and lower portion of body of hyoid bone
4–6	X. Vagus •Superiorlaryngeal branch (nerve to fourth arch) •Recurrent laryngeal branch (nerve to sixth arch)	Cricothyroid, levator palatine, constrictors of pharynx Intrinsic muscles of larynx	Laryngeal cartilages (thyroid, cricoid, arytenoid, corniculate, cuneiform)

Pharyngeal Pouch	**Derivatives**
1	Tympanic (middle ear) cavity, Auditory (eustachian) tube
2	Palatine tonsils, Tonsillar fossa
3	Inferior parathyroid gland, Thymus
4	Superior parathyroid gland,, ultimobranchial body (parafollicular [C] cells of the thyroid gland

Tongue

The tongue appears in embryos of approximately 4 weeks in the form of two **lateral lingual swellings** and one **medial swelling,** the **tuberculum impar**. These three swellings originate from the first pharyngeal arch. A second median swelling, the **copula,** or **hypobranchial eminence,** is formed by mesoderm of the second, third, and part of the fourth arch. Finally, a third median swelling, formed by the posterior part of the fourth arch, marks development of the epiglottis. Immediately behind this swelling is the **laryngeal orifice,** which is flanked by the **arytenoid swellings**.

As the lateral lingual swellings increase in size, they overgrow the tuberculum impar and merge, forming the anterior two-thirds, or body, of the tongue. Since the mucosa covering the body of the tongue originates from the first pharyngeal arch, **sensory innervation** to this area is by the **mandibular branch of the trigeminal nerve.** The body of the tongue is separated from the posterior third by a V-shaped groove, the **terminal sulcus**.

The posterior part, or root, of the tongue originates from the second, third, and part of the fourth pharyngeal arch. The fact that **sensory innervation** to this part of the tongue is supplied by the **glossopharyngeal nerve** indicates that tissue of the third arch overgrows that of the second.

Thyroid Gland

The thyroid gland appears as an epithelial proliferation in the floor of the pharynx between the tuberculum impar and the copula at a point later indicated by the **foramen cecum**. Subsequently the thyroid descends infront of the pharyngeal gut as a bilobed diverticulum.

During this migration, the thyroid remains connected to the tongue by a narrow canal, the **thyroglossal duct.** This duct later disappears. With further development, the thyroid gland descends in front of the hyoid bone and the laryngeal cartilages. It reaches its final position in front of the trachea in the seventh week. By then it has acquired a small median isthmus and two lateral lobes. The thyroid begins to function at approximately the end of the third month, at which time the first follicles containing colloid become visible. **Follicular cells** produce the colloid that serves as a source of **thyroxine** and **triiodothyronine. Parafollicular,** or **C, cells** derived from the **ultimobranchial body** (F serve as a source of calcitonin.

Face

At the end of the fourth week, **facial prominences** consisting primarily of neural crest-derived mesenchyme and formed mainly by the first pair of pharyngeal arches appear. **Maxillary prominences** can be distinguished lateral to the stomodeum, and **mandibular prominences** can be distinguished caudal to this structure. The **frontonasal prominence,** formed by proliferation of mesenchyme ventral to the brain vesicles, constitutes the upper border of the stomodeum. On both sides of the frontonasal prominence, local thickenings of the surface ectoderm, the **nasal** (**olfactory**) **placodes,** originate under inductive influence of the ventral portion of the forebrain.

During the fifth week, the nasal placodes invaginate to form **nasal pits.** In so doing, they create a ridge of tissue that surrounds each pit and forms the **nasal prominences.** The prominences on the outer edge of the pits are the **lateral nasal prominences;** those on the inner edge are the **medial nasal prominences.**

During the following 2 weeks, the maxillary prominences continue to increase in size. Simultaneously, they grow medially, compressing the medial nasal prominences toward the midline. Subsequently the cleft between the medial nasal prominence and the maxillary prominence is lost, and the two fuse. Hence, the upper lip is formed by the two medial nasal prominences and the two maxillary prominences. The lateral nasal prominences do not participate in formation of the upper lip. The lower lip and jaw form from the mandibular prominences that merge across the midline. Initially, the maxillary and lateral nasal prominences are separated by a deep furrow, the **nasolacrimal groove**. Ectoderm in the floor of this groove forms a solid epithelial cord that detaches from the overlying ectoderm. After canalization, the cord forms the **nasolacrimal duct;** its upper end widens to form the **lacrimal sac.** Following detachment of the cord, the maxillary and lateral nasal prominences merge with each other. The nasolacrimal duct then runs from the medial corner of the eye to the inferior meatus of the nasal cavity, and the maxillary prominences enlarge to form the **cheeks** and **maxillae.** The **nose** is formed from five facial prominences: the frontal prominence gives rise to the bridge; the merged medial nasal prominences provide the crest and tip; and the lateral nasal prominences form the sides.

Intermaxillary Segment

As a result of medial growth of the maxillary prominences, the two medialnasal prominences merge not only at the surface but also at a deeper level. The structure formed by the two merged prominences is the **intermaxillary segment.** It is composed of
(*a*) a **labial component,** which forms the philtrum of the upper lip;
(*b*) an **upper jaw component,** which carries the four incisor teeth; and
(*c*) a **palatal component,** which forms the triangular primary palate. The intermaxillary segment is continuouswith the rostral portion of the **nasal septum,** which is formed by the frontal prominence

Secondary Palate

Although the primary palate is derived from the intermaxillary segment, the main part of the definitive palate is formed by two shelf like outgrowths from the maxillary prominences. These outgrowths, the **palatine shelves,** appear in the sixth week of development and are directed obliquely downward on each side of the tongue. In the seventh week, however, the palatine shelves ascend to attain a horizontal position above the tongue and fuse, forming the **secondary palate**. Anteriorly, the shelves fuse with the triangular primary palate, and the **incisive foramen** is the midline landmark between the primary and secondary palates. At the same time as the palatine shelves fuse, the nasal septum grows down and joins with the cephalic aspect of the newly formed palate.

C L I N I C A L C O R R E L A T E S

Facial Clefts

Cleft lip and cleft palate are common defects that result in abnormal facial appearance and defective speech. The **incisive foramen** is considered the dividing landmark between the **anterior** and **posterior** cleft deformities. Those anterior to the incisive foramen include **lateral cleft lip, cleft upper jaw,** and **cleft** between the **primary and secondary palates**. Such defects are due to a partial or complete lack of fusion of the maxillary prominence with the medial nasal prominence on one or both sides. Those that lie posterior to the incisive foramen include **cleft** (**secondary**) **palate** and **cleft uvula**. Cleft palate results from a lack of fusion of the palatine shelves, which may be due to smallness of the shelves, failure of the shelves to elevate, inhibition of the fusion process itself, or failure of the tongue to drop from between the shelves because of micrognathia. The third category is formed by a combination of clefts lying anterior as well as posterior to the incisive foramen. Anterior clefts vary in severity from a barely visible defect in the vermilion of the lip to extension into the nose. In severe cases the cleft extends to a deeper level, forming a cleft of the upper jaw, and the maxilla is split between the lateral incisor and the canine tooth. Frequently such a cleft extends to the incisive foram. Likewise, posterior clefts vary in severity from cleavage of the entire secondary palate to cleavage of the uvula only.

Oblique facial clefts are produced by failure of the maxillary prominence to merge with its corresponding lateral nasal prominence. When this occurs, the nasolacrimal duct is usually exposed to the surface.

Median cleft lip, a rare abnormality, is caused by incomplete merging of the two medial nasal prominences in the midline. This anomaly is usually accompanied by a deep groove between the right and left sides of the nose Infants with midline clefts are often **mentally retarded** and may have brain abnormalities that include varying degrees of loss of midline structures. Loss of midline tissue may be so extensive that the lateral ventricles fuse (**holoprosencephaly**). These defects are induced very early in development, at the beginning of neurulation (days 19–21) when the midline of the forebrain is being established.

Most cases of cleft lip and cleft palate are multifactorial. Cleft lip (approximately 1/1000 births) occurs more frequently in males (80%) than in females; its incidence increases slightly with maternal age, and it varies among populations. If normal parents have one child with a cleft lip, the chance that the next baby will have the same defect is 4%. If two siblings are affected, the risk for the next child increases to 9%. If one of the parents has a cleft lip and they have one child with the same defect, the probability that the next baby will be affected rises to 17%.

The frequency of isolated **cleft palate** is much lower than that of cleft lip (1/2500 births), occurs more often in females (67%) than in males, and is not related to maternal age. If the parents are normal and have one child with a cleft palate, the probability of the next child being affected is about 2%. If, however, there is a similarly affected child and a relative or parent both with a cleft palate, the probability increases to 7% and 15%, respectively. In females, the palatal shelves fuse approximately 1 week later than in males. This difference may explain why isolated cleft palate occurs more frequently in females than in males. **Anticonvulsant drugs,** such as **phenobarbital and diphenylhydantoin,** given during pregnancy increase the risk of cleft palate.

Nasal Cavities

During the sixth week, the nasal pits deepen considerably, partly because of growth of the surrounding nasal prominences and partly because of their penetration into the underlying mesenchyme.

At first the **oronasal membrane** separates the pits from the primitive oral cavity by way of the newly formed foramina, the **primitive choanae**. These choanae lie on each side of the midline and immediately behind the primary palate. Later, with formation of the secondary palate and further development of the primitive nasal chambers, the **definitive choanae** lie at the junction of the nasal cavity and the pharynx.

Paranasal air sinuses develop as diverticula of the lateral nasal wall and extend into the maxilla, ethmoid, frontal, and sphenoid bones. They reach theirmaximum size during puberty and contribute to the definitive shape of the face.