The purpose of this chapter is to present concepts of cleft palate repair based on a single unifying concept: the embryology of the oronasopharynx. We shall begin with an in-depth discussion of how the bone and soft tissue structures are assembled, based upon the developmental field model. Next, we shall consider how this normal process is altered when a disruption of the neurovascular pedicle to an individual field results in a deficiency state such that the affected field is unable to fuse with its partner fields. Attention will also be given to the effect that such a deficiency state has on the subsequent development of the partner fields. Surgical procedures based on the embryologic model are designed to restore functional tissue relationships.

Craniofacial development: the Lego® model

The anatomic structures of the head and neck are assembled from tissue units known as developmental fields, each of which has a distinct neurovascular pedicle providing sensory and/or autonomic control and blood supply. Fields are often composite structures containing mesenchymal elements such as cartilage, bone, fascia, muscle and so on. They may have an associated epithelium such as skin or mucosa. Adjacent fields interact. Muscles with a primary attachment to bone or cartilage within one field may have a secondary attachment site in an adjacent field.

Fields develop in a strict spatio-temporal sequence. Congenital conditions that reduce the size or content of a field will affect subsequent growth. In the Pierre Robin sequence, the relative decrease in volume of the mandibular ramus leads to a posterior position of the chin and subsequent relationships of the infrapharyngeal musculature. The reduction of the frontal process of the premaxilla seen in the typical orofacial cleft causes a relative narrowing of the nasal fossa, malposition of the internal nasal valve, and respiratory dysfunction (Figure 1.1).

The anatomic defects seen in clefts of the hard and soft palate present as a spectrum involving several fields. Many cases involve deficiency states of the piriform fossa and/or premaxilla and soft tissues of the lip and nose. In other, rarer conditions, such as the Tessier 3 cleft, a cleft palate defect coincides with defects in seemingly unrelated anatomic zones, such as the inferior turbinate and medial maxillary wall. For this reason, it is necessary to have a comprehensive picture of the neurovascular anatomy of the oronasopharynx.

The zones of anatomic interest are all supplied by arterial axes running in parallel with the various sensory branches of V1 and V2. Development of the pedicles is a reciprocal process. Neuronal growth cones secrete vascular endothelial growth factor (VEGF) while the arterial growth cone secretes nerve growth factor (NGF). Like all cranial nerves, the trigeminal complex is constructed from neural crest, whereas the histologic composition of the arteries consists of a tubular conduit of endothelial cells made from paraxial mesoderm embraced by pericytes. These latter cells are contractile and control capillary permeability. Pericytes are ubiquitous throughout the human body (Figure 1.2). They are the precursor for mesenchymal stem cells. They also elaborate paracrine factors that are essential for survival of the vascular growth cone. Thus, we come to a very simple and powerful idea: dysfunction of a vascular growth cone will result in either a reduction of volume of mesenchymal structures within the target field, or the outright loss of the field itself. In the first case, the physical effect of the small field is to constrain subsequent growth of surrounding fields. If a frank tissue defect exists (i.e., a cleft) adjacent fields actually collapse into the site.

The reader will note here terminology that may be unfamiliar: it harkens back to those embryology lectures that we endured … an endless list of structures that morphed into a final result via mechanisms that were unknown. The molecular revolution transformed the science into developmental biology with a
Craniofacial fields are composite blocks of tissue supplied by a specific neurovascular pedicle. Fields grow in relation to each other over time, each with a different volume and rate of growth. Deficiency or absence of a field results in collapse of adjacent partner fields. The leaning tower of Pisa is a classic example of what happens when a supporting field is absent—the entire complex is displaced and, if the upper stories of the tower were made of soft plastic, would become distorted as well. A “cleft” is really a condition of excess or deficiency in a given field that results in displacement and/or distortion of adjacent fields.

The embryonic period lasts 8 weeks and is divided into 23 anatomic stages (see Figure 1.3). In the first three stages, the embryo is a rapidly dividing ball of cells. Stages 4–5 are all about survival as the embryo implants itself into the uterine wall and begins the process by which blood supply will come from the mother. The stage 4 embryo secretes fluid into its center, becoming a hollow blastocyst with a single layer of cells, the epiblast, becoming segregated to one side of the ball. Thus there is an inner cell mass (the future organism) and an enveloping wall (the trophoblast) that will eventually form the extraembryonic structures, such as the placenta (O’Rahilly & Müller, 1996). The tightly-bound cells of the epiblast then become transiently “loose,” allowing some of the epiblast cells to drop down below their previous plane, coalesce and form a new second layer, the hypoblast. By the end of stage 5, the hypoblast has proliferated and formed a lining layer around the inner wall of the trophoblast. The hypoblast now secretes a new layer, extraembryonic mesoderm (EEM), interposed between it and the trophoblast. This geometry allows the EEM to surround the entire embryo and move into the zone of the future placenta. Since blood vessels are formed exclusively from mesoderm, the EEM becomes the source for the entire extraembryonic blood supply.

Stages 6–7 involve a transformation of the intraembryonic tissues into three layers (ectoderm, mesoderm, and endoderm) via a process called gastrulation: “the single most important event in the life of every organism.” There are excellent videos of gastrulation available on YouTube. Note that at the completion of gastrulation, the hypoblast is pushed out of the way; it has no role in the formation of the organism per se. In point of fact, the epiblast contributes first to endoderm, then to mesoderm. When the gastrulation process is complete, the cells remaining behind on the surface are known as the ectoderm proper.

The concept of three germ layers is outmoded and inapplicable to understanding craniofacial development. For simplicity, let’s leave the epithelial germ layers (ecto- and endoderm) behind and concentrate on mesoderm. This layer outside the head and neck is responsible for all striated muscles, bone, cartilage, brown fat (white fat is more complex), fascia, and the non-neural internal organs. Furthermore, as mesoderm fans out over the surface of the embryo, its identity becomes determined by the interplay of gene products expressed either from the midline (i.e., the neural tube) such as sonic hedgehog (SHH) and wingless (WNT) or from the peripheral epithelial surfaces of future skin (ectoderm) and mucosa (endoderm) such as BMP-4 (Carstens, 2000, 2002).

Depending upon location, mesoderm assumes three basic fates. Paraxial mesoderm (PAM) lies next to the neural tube. It becomes segmented into individual tissue blocks called somites, each one of which is developmentally related to the segment of the nervous system from which it derives its innervation. Somites construct the entire axial skeleton, related striated muscles, and the major axial arteries (aorta, carotids, etc.). Intermediate mesoderm (IM) is also segmentally organized; it forms the genito-urinary system. Finally, lateral plate mesoderm (LPM) forms the entire appendicular skeleton, the remainder of the arteries, smooth muscle, and the viscera (Carstens, 2008a, 2008b) (Figure 1.4).

Left out from this equation is the fourth germ layer, the neural crest. The vast majority of all facial soft tissues in the face and all the craniofacial membranous bones arise from neural crest. These cells substitute for mesoderm in the head. They also form the ensheathing Schwann cells of the peripheral nervous system and the entire autonomic nervous system.

During stages 8–9 neurulation takes place. First, a flat neural plate is formed; this then rolls up like a cigar to form the neural tube. Neural crest cells develop at the interface between the overlying ectoderm and the neural plate. These rapidly multiply and are distributed over the entire organism, immediately subjacent to the epithelia (ectoderm and endoderm) and throughout the
mesoderm. Neural crest cells are critical for craniofacial development (Figure 1.5).

Stages 8–9 are also notable for the segmentation of the zone of paraxial mesoderm flanking the neural tube. PAM forms into distinct blocks called somites. There are names for their respective locations: 4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 3–4 coccygeal. The appearance of the first three occipital somites alongside the hindbrain defines stage 9. Somitogenesis is a cranial-caudal process in which one somite appears approximately every 4 hours (Figure 1.6). However, there is an additional zone of PAM which lies cranial to the somites alongside the midbrain and forebrain in which the segmentation is incomplete, forming seven somitomeres. Somitomeres (Sms) have very limited developmental potential. They produce the striated muscles of the orbit and the first three pharyngeal arches; Sm1 and Sm2 also contribute to the posterior wall of the orbit.

So what we have now is a critical mass of tissues that will mix together to form a series of five intermediate structures, the pharyngeal arches, each of which is innervated by a specific cranial nerve. These structures first develop at a stage when the embryo is still flat; at stage 9 the embryo begins a complex folding process. The first pharyngeal arch can be seen at this stage. It hangs downward like a sock filled with neural crest and PAM. At each stage thereafter a new pharyngeal arch makes its formal appearance. The process of making the five pharyngeal arches is thus complete by stage 14 (Figures 1.7 and 1.8). All pharyngeal arches are organized into distinct zones by a series of distal-less (Dlx) genes: proximal/distal, cranial/caudal, and medial/lateral. All arches have the same organizational pattern.
At stage 5, 9–10 days, the embryo is a hollow ball (blastocyt) consisting of the embryo proper surrounded by trophoblast (green) that will eventually make non-embryonic tissues such as the placenta. From the original inner cell mass a second layer of cells develops beneath. The embryo now has an epiblast (blue), and a hypoblast (yellow), also termed the primitive endoderm. Hypoblast spreads out to line the entire blastocyst cavity. It then secretes the primitive mesoderm (red) which will flow up into the future placenta and make the extra-embryonic circulation.

Arch 1 has a rostral maxillary zone innervated by V2 and a caudal mandibular zone supplied by V3. Muscles of mastication in the first arch all arise from somitomere 4. Arch 2 fuses with arch 1; it contains the muscles for facial expression. The upper division of VII supplies facial muscles from somitomere 5 distributed over the maxillary zone while the lower division of VII innervates muscles from somitomere 6 distributed over the mandible (see Figure 1.9).

Embryonic folding driven largely by explosive brain growth causes the pharyngeal arches to swing upward into the adult position. They subsequently fuse. Growth of the vascular channels into the arches proceeds concomitant with penetration of the arches by cranial nerves from the brain. We will now briefly explore how the individual neurovascular pedicles associated with the nasopharynx and oropharynx are organized. This will give us insight into the manner in which the developmental fields are assembled (O’Rahilly & Müller, 1999).

The final configuration of craniofacial arteries is the result of a step-wise process by which primitive structures meld into more complex forms. Arteries are mesodermal structures, the earliest ones appear after gastrulation is complete. The forebrain and midbrain are supplied by a primitive head plexus while primitive hindbrain channels supply the remainder of the brain. The dorsal aortae run alongside the body axis and supply non-neural tissues. Anterior extensions of the dorsi aortae connect with one another anterior to the brain and to the oropharyngeal membrane, greater complexity is assumed. The arteries to the brain and spinal cord assume a segmental pattern to supply each developmental unit of the CNS, that is neuromeres. Each of the five pharyngeal arches is supplied by a segmental aortic arch artery connecting the primitive outflow tract with the paired dorsal aortae above. The fifth aortic arch artery atrophies with AA4 supplying both pharyngeal arch 4 and 5. AA6 is dedicated exclusively to the pulmonary circulation (Figures 1.10–1.12).

Figure 1.4 (a) Note here that the primitive endoderm/hypoblast (green) will be pushed out of the way by the definitive endoderm (yellow). Hypoblast thus has no biologic role in development other than to serve as a temporary layer. (b) Mesoderm will have specific roles depending upon its location in the embryo. This is because at each physical location a unique combination of gene products from ectoderm and endoderm act as signals to the mesoderm, “instructing” it as to its ontogenic fate. Paraxial mesoderm (red) forms: somites, dermis, striated muscle, the axial skeleton. Intermediate mesoderm (not seen) is a long thin rod of tissue extending along the axis of the embryo. It is neuromerically organized. It produces the entire genito-urinary system. Lateral plate mesoderm (purple) forms: the cardiovascular system, smooth muscle, the appendicular skeleton, and the mesenchyme for all internal organs.
Mechanisms of cleft palate: developmental field analysis

(a) Neuromeres are developmental units of the nervous system, the boundaries of which are established by unique combination of products from homeotic genes (Hox). In humans there are 38 Hox genes distributed over four chromosomes. Common to each is a 60 amino acid sequence that unlocks DNA. Hox genes code for the CNS as far forward as the midbrain/hindbrain junction. Recently discovered additional Hox-related genes code for the neuromeres of the midbrain and forebrain. Carlson BM. Human Embryology and Developmental Biology, 3rd edn. Reproduced with permission of Elsevier. (b) Neural crest at any given level of the CNS has exactly the same Hox code as the neuromere above which it originates. Color coding shows contributions as follows. PROSENCEPHALON (forebrain) = pink. Non-neural ectoderm (not truly neural crest) lies above prosomeres p5 and p6. P6 produces the nasopharyngeal mucosa supplied by V1. P5 produces the epidermis supplied by V1. Prosomeres p4-p1 are unclear but probably flow beneath p6 and p5 to produce (respectively) nasopharyngeal submucosa and dermis. MESENCEPHALON (midbrain) = red. M1 goes to membranous bone. M2 goes to meninges, orbit, and first arch. First arch contains m2, r1, r2, and r3; second arch contains r4 and r5; third arch has r5 and r6; fourth arch has r7 and r8. NB: each arch has a longitudinal axis with equal numbers of neuromeres represented on either side. The coordinates of the arches are determined by the distal-less (Dlx) system of genes.

Within the pharyngeal arches, the aortic arch arteries constitute primitive vascular cores. These rapidly involute, each one being replaced with a plexus, the confluence of which forms the external carotid system. At Carnegie stage 17 an entirely new system of stapedial arteries develops, the initial stem of which runs upward from internal carotid through the temporal bone. The timing of stapedial development precisely matches the emergence of the cranial nerves, each nerve serving as the template for a respective artery. These dural arteries connect externally to the external carotid system via the trigeminal ganglion. In the orbit the V1-related stapedial (StV1) plugs into the ophthalmic. The latter supplies the ocular apparatus while the former supplies all the periorbital structures (muscle, fascia, bone, etc.). When the parent stem of stapedial involutes, the final anatomy takes shape: the dural arteries are now supplied

Figure 1.6 Somitomeres and somites develop from paraxial mesoderm. Somitomeres are hollow balls with a somitocoele in the center; they are incompletely separated from each other, so mesenchyme can be shared. Somites are discrete units with epithelial boundaries. They have regional specializations for axial bone (sclerotome), muscle (myotome), and epaxial dermis (dermatome). Humans have 7 somitomeres and 39 somites. The process of somitogenesis in mammals takes approximately 4 hours per somite. Gilbert SF, Developmental Biology, 10th edn., Sinauer, 2014. Sinauer Associates, Inc.

Figure 1.7 Only four arches (the fifth is diminutive) and no sixth arch. Aortic arch arteries span the four arches, AA4 supplying pharyngeal arch 5. Arteries to the sixth “arch” are dedicated to pulmonary circulation. http://creatureandcreator.ca/. Reproduced with permission of Terry Picton. Last accessed December 2014.
by the external carotid system. The ophthalmic is a hybrid; the original stem from the internal carotid is dedicated to the eye while StV1 serves the orbital structures exclusively (Figures 1.13 and 1.14).

The extension of the stapedial downward through the trigeminal ganglion gives it access to the distal extent of the external carotid system, to which it attaches just beyond the take-off of the facial artery. Those branches associated with StV2 supply the maxilla. Each of these is distributed through the pterygopalatine plexus while StV3 supplies the mandible.

Developmental fields of the naso-oropharynx containing membranous bones

We come now to the crucial concept. Each of the StV2 branches is responsible for supplying one or more fields within the maxilla. Thus, a reduction or knock-out in any one of these branches will create a tissue deficiency state (cleft). Each of the Tessier cleft zones contains specific bone and cartilagenous structures. Thus, it is possible to use the reduction in size or absence in a marker structure to define the presence of a Tessier cleft.

- Internal medial nasal (StV1), Tessier zone 1: nasal bones and upper septum.
- External medial nasal (anterior ethmoid) (StV1), Tessier zone 1: distally these extend down through the columella and into the philtrum. Collaterals to central incisor.
- Internal lateral nasal (StV1), Tessier zone 3: upper turbinate and middle turbinate.
- External lateral nasal (StV1), Tessier zone 4: piriform fossa.
- Lacrimal (StV1), Tessier zone 9: lateral orbit – anastomoses with orbital branch of middle meningeal.
- Supraorbital (StV1), Tessier zone 10–11.
- Supratrochlear artery (StV1), Tessier zones 12–13.
- Medial nasopalatine (StV2), Tessier zone 2: lower septum, vomer, and premaxilla.
- Lateral nasopalatine (StV2), Tessier zone 3: inferior turbinate, medial maxillary wall, and the nasal mucosa of the secondary hard palate.
- Descending palatine (StV2), Tessier zone 3: palatine bone, oral mucosa of the secondary hard palate.
- Medial infraorbital (anterior alveolar) (StV2), Tessier zone 4: frontal process of maxilla, canine, anterior maxilla medial to the foramen.
- Lateral infraorbital artery (middle alveolar) (StV2), Tessier zone 5: premolars, anterior maxilla lateral to foramen.

![Figure 1.9](image) Mesoderm from the first seven somitomeres has a very limited role in craniofacial development. Somitomere 4 supplies the muscles of mastication. Somitomeres 5–6 supply the muscles of facial expression. Somitomere 7 supplies all muscles of the palate except the tensor. Adapted from Butler AB, Hodos W. *Comparative Vertebrate Neuroanatomy*, 2nd edn., Wiley-Liss, 2005. Reproduced with permission of John Wiley & Sons.
Mechanisms of cleft palate: developmental field analysis

- Posterior alveolar (StV2), Tessier zone 6: molars, posterior maxillary wall.
- Zygomatico - facial (StV2), Tessier zone 7: malar bone (lower zygoma).
- Zygomatico - temporal (StV2), Tessier zone 8: post-orbital bone (upper zygoma).
  (NB: Tessier zone 9 is the rarest cleft, most likely because of its dual blood supply – the anastomosis between the lacrimal and zygomatico-temporal.)

All of the above fields contain one or more membranous bones, all of which are derived from neural crest. (NB: in craniofacial development the only bones that are derived from mesoderm (lateral plate) are the basisphenoid, part of the temporal bone, and the occipital bone complex below the superior nuchal line. All remaining bones arise from neural crest.)

Developmental fields of the 
naso-oropharynx containing muscle

What about fields that are composed exclusively of muscle? This would include the muscles of the soft palate and pharynx. How do we categorize their blood supply? What could go wrong in development to produce the pathologies associated with cleft palate?

The physiology of speech depends upon muscles that are both intrinsic to the soft palate and those that are extrinsic to it. The following concepts are essential for understanding the developmental anatomy of this integrated muscle system.

1. Craniofacial muscles arise from paraxial mesoderm (PAM).
2. PAM is segmentally organized into 7 somitomeres and 35 somites. The process of mesoderm segmentation takes place during stages 7–8 and proceeds in a cranio-caudal direction. Each segment will be supplied by a designated motor nerve.
3. Craniofacial mesenchyme is predominantly neural crest, not mesoderm. From stages 9 to 14 this mesenchyme becomes itself segmented into five pharyngeal arches.
4. Located in the core of each arch is an aortic arch artery that spans from the cardiac outflow tract located below the future pharynx to the dorsal aorta lying above the pharynx. The fifth aortic arch artery involutes and the fourth takes over the supply for the structures of both pharyngeal arches 4 and 5.
Figure 1.12 Scanning electron microscopy shows embryo in reversed position (head to right). At this stage the pharyngeal arch plexus is very dense. Just caudal to the fourth aortic arch artery, arrowheads indicate the stumps of the involuting fifth aortic arch artery. AA4 will subsequently supply both pharyngeal arches 4 and 5. There is no sixth pharyngeal arch in mammals (in fish, yes). The artery assigned to this mesenchyme, AA6, will be incorporated into the pulmonary circulation. Hiruma T. Formation of the pharyngeal arch arteries in the chick embryo. Observations of corrosion casts by scanning electron microscopy. Anat Embryol 1995; 191:415–424. Reproduced with permission of Springer Science and Business Media.

Figure 1.13 Dural arteries are all derivatives of the intracranial stapedial system. Upon involution of the stem these all form anastomoses with branches of the internal and external carotid systems. Diamond MK. Homologies of the stapedial artery in humans, with a reconstruction of the primitive stapedial artery configuration in euprimates. Am J Phys Anthro 1991; 84:433–462. Reproduced with permission of John Wiley & Sons.

(5) Despite textbook dogma, there is no sixth pharyngeal arch. The sixth aortic arch artery becomes incorporated into the pulmonary circulation.

(6) The muscles that develop within the pharyngeal arches originate from paraxial mesoderm that becomes physically incorporated into the arch system. Hypoplasia or aplasia of palate musculature can occur from an intrinsic defect of the mesoderm or from a failure of the arterial axis that supplies it. Such defects can be isolated to a single muscle or can be more global as in hemi-palate.

Craniofacial mesoderm assigned to the orbit and to the first three pharyngeal arches comes from seven somitomeres (Sm). These are incompletely separated balls of mesoderm with branches of the internal and external carotid systems. Diamond MK. Homologies of the stapedial artery in humans, with a reconstruction of the primitive stapedial artery configuration in euprimates. Am J Phys Anthro 1991; 84:433–462. Reproduced with permission of John Wiley & Sons.

The pharyngeal arch system is transient; so too are the aortic arch arteries that originally supplied each pharyngeal arch. These break down, reorganize, and eventually are connected
The pathways of extraocular muscles from somitomeres 1, 2, 3, r0/r1 soft palate muscles, bone fields from stapedial V2: vomer, premaxilla, palatal r2 primary axis of the soft palate, bone fields from stapedial V3: mandible. secondary axes of the soft palate are: r5 bone fields from stapedial V1: perpendicular plate of neural crest to arterial wall of ascending palatine branch. nerve XI. The reason for the overlap between cranial nerves IX and XI is that they are in register with the same zone of the brain stem; their nuclei simply represent two parallel columns reflecting different functions. The constrictors are likely to arise from somites 2 and 3; their motor supply is cranial nerve XI. Stylopharyngeus relates to the second arch and therefore is likely to arise from somitomere 5 (or 6). Salpingopharyngeus relates to the portion of the tympanic tube that is developmentally related to the third arch; thus it likely comes from somitomere 7.

Knowing the above facts, we can make some general statements about muscle pathologies in cleft palate. All defects of the hard palate, either primary (the premaxilla), from the incisive foramen forward, or secondary, from the incisive foramen backward, involve deficiencies in membranous bone. These are readily diagnosed by physical examination and 3D CT scanning. Such bone defects involve one or more arterial axes of the StV2 stapedial system supplying the maxilla. The nucleus of V2 resides within the second rhombomere of the hindbrain (r2). Thus defects of the maxillary complex represent deficiencies in the population of neural crest cells arising from that segment of the neural fold in genetic register with r2. Strictly by logic a bone defect occurs when something is intrinsically wrong with the r2 mesenchymal population or there is defective formation of a neurovascular axis supplying a portion of the r2 population. The latter mechanism is more specific; it explains isolated bone defects at later stages in development rather than a global failure of neural crest mesenchyme in the first arch.

Mandibular defects associated with cleft palate, as in the Pierre Robin sequence, can be diagnosed in a similar way. Defects involving any developmental zone of the mandible involve one or more arterial axes of the StV3 stapedial system. The nucleus of V3 resides within the third rhombomere of the hindbrain (r3). Thus, defects of the mandibular complex represent deficiencies in the population of neural crest cells arising from that segment of the neural fold in genetic register with r3. Tensor veli palatini is the sole palate muscle belonging to the first arch; it comes from somitomere Sm4 (which also bears the muscles of mastication). For this reason, any form of cleft palate involving TVP implies a more proximal “hit” to the StV2–StV3 system or a more global involvement of first arch neural crest.

**Summary of neural crest and mesodermal derivatives that contribute to cleft palate**

- r0/r1 = bone fields from stapedial V1: perpendicular plate of the ethmoid, septum, columella, prolabium.
- r2 = bone fields from stapedial V2: vomer, premaxilla, palatal shelf, inferior turbinate.
- r3 = bone fields from stapedial V3: mandible.
- r5 = neural crest to arterial wall of ascending palatine branch of facial > soft palate muscles.
• \( r7 \) = neural crest to arterial wall of ascending pharyngeal to soft palate/pharynx muscles.
• \( Sm4 \) = mesoderm of tensor veli palatini.
• \( Sm7 \) = mesoderm of levator veli palatini, palatoglossus, palatopharyngeus, uvulus.

**Mechanisms of developmental field failure**

Now that we have an idea of the various neurovascular axes, let us consider a first mechanism of failure, alteration of function of the growth cone. Because growth of the axes proceeds outward, the earlier in time the failure occurs the more structures will be affected. For example, the premaxilla is the terminal field for the medial nasopalatine axis. It has three sub-fields: the central incisor, lateral incisor, and the frontal process of the premaxilla (which lies tucked beneath the frontal process of the maxilla). Any perturbation of the nasopalatine axis will show up first as a deformation in the inferolateral rim of the piriform fossa. Next the lateral incisor and its bony housing are affected. Finally, a total loss of premaxilla can occur (Figure 1.16).

A simplifying concept involves failure of the vascular growth cone (Figures 1.17 and 1.18). The growth cone of the artery consists of an endothelial tip sprout that produces PDGF-B which is chemoattractive for pericytes and positive for the receptor PDGFR\( \beta \). These cells distribute themselves along the abluminal wall of the vessel along which they secrete cytoplasmic processes.

We turn our attention to the specific anatomic variations of cleft palate. We postulate that fusion of these mesenchymal tissue units (partner fields) requires that they be physically positioned relative to each other within a critical contact distance. If the tissue volume of one of the fields is reduced, and the critical contact distance is exceeded, fusion will not occur and a cleft will result. A second mechanism involves the alteration of fusion potential of the epithelial surface. The stability of the epithelium is controlled by sonic hedgehog (SHH). As long as this is active, the epithelial surface will be incapable of fusion. SHH is itself inhibited by BMP-4 of the underlying mesenchyme. The total amount of BMP-4 produced by a field is proportional to its mesenchymal volume. Thus, any reduction in BMP-4 production will promote the stability of the epithelial surface and prevent its fusion.

![Figure 1.16](image-url) The alveolar walls of the premaxilla (PMx) are supplied by medial nasopalatine artery; the labial alveolar wall receives collateral supply from the medial infraorbital. Premaxilla has three subfields: the medial incisor, lateral incisor, and the frontal process. Since the frontal process is the most distal, it is always affected first in deficiency states. Bartezko K, Jacob M. A re-evaluation of the premaxillary bone in humans. *Anat Embryol* 2004; 207:417–437. Reproduced with permission of Springer Science and Business Media.
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Figure 1.17 Schwann cells pick up nutrients and growth factors from the environment and transmit them back into the axon. NGF (nerve growth factor) produced by the pericytes promotes growth of the neural axis in register with the vascular axis. Adapted from: May F et al. Nerve replacement strategies for cavernous nerves. *Europ Urol* 2005; 48:372–378.

Figure 1.18 Vascular endothelial growth factor (VEGF) produced by the nerve cone causes outgrowth of endothelial cells from a vascular axis. These endothelial cells form the core of the new vessel or they add on to an existing vessel to elongate it. But stabilization of the new vessel by pericytes is now required. Tip cells produce PDGF-B that recruits pericytes to come alongside the endothelial axis and stabilize it. Adapted from: Quaegebeur A, Lange C, Carmeliet P. The neurovascular link in health and disease: molecular mechanisms and therapeutic implications. *Neuron* 2011; 71:406–424. Reproduced with permission of Elsevier.

Fusion of the palate is bi-directional, proceeding both forward and backward from the incisive foramen. Closure of the primary palate involves interaction between the alveolar processes of the premaxilla (medial nasopalatine artery) and the canine-bearing mesial maxilla (lateral nasopalatine artery). In addition, the frontal process of premaxilla fuses with the overlying frontal process of the maxilla. This latter structure is supplied by the medial branch of the infraorbital and belongs to the Tessier cleft zone 4.

Fusion of the secondary hard palate takes place concomitantly. It involves union between the vomer and the horizontal palatal shelf. The vomer is the proximal tissue field along the medial
nasopalatine shelf. Its partner field, the horizontal palatine shelf, is actually supplied by two distinct neurovascular axes: lateral nasopalatine on the nasal side and greater palatine artery on the oral side. Sinus formation within the horizontal shelf has been previously reported. All sinuses represent the separation of adjacent fields from one another.

It is useful to think of field development as a flow of mesenchyme into a geometric space. Flow into the palatal shelf appears to follow an anterior-to-posterior gradient. Thus, insufficiency will always manifest itself in the “newest” zone, that is, posteriorly. The fusion process of the secondary hard palate is anterior-to-posterior.

Cleft palate: analysis by zones

Tessier cleft zone 14: a misleading concept

The zone does not exist. This was a trompe l’oeil for Tessier. The frontal bone is not singular; it is two halves which fuse in the midline. Each hemi-frontal bone is a bilaminar structure with four developmental fields, all of which are organized around four StV1 neurovascular axes. Zones 13 and 12 are supplied by the supraorbital externally and internally these zones are supported by the medial meningeal flowing over the ethmoid plate. Zones 11 and 10 are supplied externally by the supraorbital, while internally the lacrimal supplies the lateral orbital. Development of the frontal bone takes place by the membranous ossification of the neural crest which migrates from rhombomere 0 (zones 13–12) and from rhombomere 1 (zones 11–10). This ectomesenchyme follows a pathway alongside the midbrain and forebrain, forward over the orbit and downward to form the nasal process. This mesenchyme is the source of the dura and dermis within which the membranous bone fields develop. The neural crest populates and pushes forward a unique ectodermal envelope which is described below (Figure 1.19).

The epidermis of the zones overlying the forehead and nose is likewise unique. As the r0/r1 neural crest flows forward it tracks beneath the overlying non-neural ectoderm to produce the skin of the V1 region. Non-neural ectoderm (NNE) is a layer of tissue overlying the prosencephalon (forebrain). NNE acts like ectoderm; it is in genetic register with the six underlying prosomeres of the forebrain (p1–p6). The interaction between the r0/r1 beneath the NNE covering the most rostral prosomeres, p5 and p6, produces frontonasal skin, a structure radically different from the remainder of facial skin and body. (NB: The reader will recall that the source of dermis of all head and neck skin down to the level of C2 is not mesodermal, but neural crest.) For this reason, in frontonasal dysplasia the skin appears different in thickness and consistency.

Closure of the frontal bone zones takes place by a process of apoptosis, a controlled breakdown of tissue that allows the frontal fields to move forward into the midline. Of course, the driving force for this is the medialization of the orbits, a process that is dictated by the growth pattern of the brain and the anterior cranial base. The ethmoid complex is interposed between the orbits. Failure of apoptosis in the ethmoid zones will lead to hypertelorism. Since the ethmoid is a bilateral structure, such hypertelorism can be unilateral or bilateral. Probably the apoptosis process required of the frontal bone is subject to whatever degree of apoptosis is taking place in the ethmoid complex.

Midline pathologies can manifest as a simple excess of tissue or as a fusion failure or cleft (sic). For this reason, it appeared to Tessier as if this were truly an autonomous zone. Recall that the pituitary sits in a cavity between two bones: the anterior neural crest presphenoid and a posterior mesodermal post-sphenoid

Figure 1.19 (a) Non-neural ectoderm overlying prosomeres p5 (blue) and p6 (red) is not formally neural crest; it is responsible for the frontonasal epidermis. Frontonasal dermis results from sub-epidermal forward flow of more posterior neural crest. (b) Note neural crest contributions to craniofacial arterial systems. Etchevers HC, Couly G, Le Douarin NM. Morphogenesis of the branchial vascular sector. Trends Cardiovasc Med 2002; 12(7):299–306. Reproduced with permission of Elsevier.
Mechanisms of cleft palate: developmental field analysis

(basisphenoid). The former has a sinus while the latter is solid. Fusion failures extending backward into the sphenoid have a biologic limit to viability. Failure of apoptosis in the midline of zone 13 also leads to a residual excess of mesenchyme in the midline; this is normal orbital approximation and results in hypertelorism.

Medialization can also be altered by the presence of an encephalocele that can seek out a field failure between any of the zones to achieve an extracranial position and thereby block the closure. The escape routes of encephalocoeles are well documented, be they forward through the frontal bone zones, in the midline or in paramedian positions.

**Neuroembryologic simplification of zones 1 and zone 13/zone 2 and zone 12**

Tessier originally perceived that a fundamental difference existed between clefts (states of mesenchymal deficiency and/or excess) involving the maxilla and those involving the orbit. At the time, neuroembryology of the area was not recognized. In our correspondence, Tessier was impressed by the correlation between his findings and the regional sensory neuroanatomy (Flores-Sarnat, et al., 2007). The structures of the nose are unique in that the topology of the fields supplied by the neurovascular axes of StV1 and StV2 is not one of simple planar separation, rather these fields are *interlocking*. This makes the interpretation of congenital field defects difficult. The best way to keep things straight is for us to consider these zones by their neuroanatomy, with 1–2 supplied by StV2 axes while those of zones 13 and 12 are supplied STV1 axes. For this reason, we are going to violate the traditional way of describing Tessier clefts in this region. In the end, as he himself commented, the observations will be clearer (Ewings and Carstens, 2009).

**Tessier cleft zone 1**

Zone 1 consists of the structures in the midline of the nose and mouth, the paired vomer and perpendicular ethmoid bones. The nasal cavity is supplied by two neurovascular pedicles: StV2 medial nasopalatine axis, and StV1 internal medial nasal axis. The medial zone of dorsal nasal skin and nasal bones are supplied by the StV1 external medial nasal axis (Figures 1.20 and 1.21).

Paired medial nasopalatine arteries supply paired vomerine bones. Occasionally, these bones may fail to fuse. Alternatively, the intervomerine space may allow for the descent of a tumor or encephalocele into the oral cavity. Such situations require concomitant pathology of the perpendicular plates of the ethmoid. In the routine case, a deficiency of vomerine mesenchyme will impair the inhibition of sonic hedgehog (SHH) and thus the epithelial surface of that vomer front-to-back fusion process with the palatal shelf. If the palatal shelf is normal the cleft will be narrow (Figure 1.22). In the minimal state, the palate cleft is very posterior, at the posterior nasal spine, but as the degree of vomer deficiency increases, the palate cleft will extend forward until it reaches the incisive foramen.

When a minimal vomerine deficiency exists in isolation, the width of the palate cleft will be fairly narrow and uniform. The vomer develops in posterior-to-anterior sequence; as it does so, it descends from front to back into the palatal plane like a scimitar. Thus, the most vulnerable zone of the vomer is posterior

![Figure 1.20](image-url) The obliquely-oriented midline of the septum is a vascular interface zone between StV1 posterior and anterior ethmoid and StV2 medial nasopalatine arteries.
and inferior. Vomerine-based palate clefts can start as a poste-
rior notch in which the vomer is literally lifted upward and away
from the palatal plane. If the cleft runs all the way to the incisive
foramen, compromise of the arterial supply to the ipsilat-
eral premaxilla is likely. The differential diagnosis of these clefts
depends on whether the palatal shelf is uninvolved or involved
because, in the latter situation, the cleft is wider with the poste-
rior aspect more deficient (wider cleft). Bilateral vomer pathol-
ogy in the absence of all other field defects results in a bilateral
cleft palate that is narrow and can potentially run forward to the
incisive foramen. Note that since the vomer is a narrow struc-
ture, changes in width of the palatal cleft are due to additional
involvement of the palatal shelf based on the StV2 greater palat-
tine artery and/or (rarely) lateral nasopalatine artery.

**Tessier cleft zone 13**
Zone 13 consists of the midline structures of the cranial base and
of the forehead up to, but not including, the eyebrow. It interdig-
itates with zone 1 because it shares common arterial axes sup-
plying both structures of the upper nasal cavity and the medial
external nasal soft tissues of the nose.

Let’s begin with the internal upper medial structures of the
nasal cavity, the perpendicular plates of the ethmoid and sep-
tum. These are supplied by the posterior and anterior ethmoid
arteries. The StV1 posterior ethmoid arises within the orbit,
enters the posterior air cells and then does two things: (i) it
tracks upward through the cribriform plate and the presphenoid
to gain access to the dura mater as the meningeal branch sup-
plying the meninges over the ethmoid complex; and (ii) it enters
the nasal cavity to supply the perpendicular plate of the ethmoid
and the posterior superior septum.

Defects in the posterior ethmoid axis can selectively influence
hypertrophy or dystrophy of the ethmoid complex and conse-
quently ethmoid-based hyper/hypotelorism. A vertical deficiency
of the perpendicular plate of the ethmoid causes a *high arched palate* in which case the vomer has successfully fused with the
palatal shelves (Figure 1.23). In severe cases, a small ethmoid
can retract a normal vomer so far upward out of the palatal
plane that fusion is impossible, thereby leading to a midline cleft
palate with foreshortening of the vomer. Diagnosis of the latter
condition depends upon the physical size of the vomer discerned
either by inspection or using a 3D CT scan.

The StV1 anterior ethmoid artery enters from the orbits to
supply the anterior and middle ethmoid air cells and thence pro-
cceeds to supply the frontal sinus. It has three destinies.
It tracks upward through the cribiform plate to supply the dura underlying zones 13 and 12.

Internal nasal branches descend medially over the anterior superior septum and laterally to supply the superior and middle turbinate. Defects in this axis explain ipsilateral ethmoid hypertrophy and hypotrophy and consequent changes in orbital position and/or dystopias. They also can explain warping or absence of the septum.

The anterior ethmoid supplies the nasal bone from its internal surface. A defect here can cause absence of the nasal bone. The artery emerges between the nasal bone and the upper lateral cartilage to run forward and downward. A defect in this part of the axis causes the nasal skin cleft noted by Tessier in zone 1. Its terminus follows along the upper and caudal border of the septum to supply columella and prolabium. Defects in this part of the axis are responsible for rare cases of absent columella, with or without affectation of the prolabium. Note that the prolabium is generally autonomous as it gets a collateral supply from a branch of medial nasopalatine that penetrates through the premaxilla to enter the prolabium from below.

The intracranial anatomy of zone 13 is of great importance. The StV1 ethmoid branch of the anterior ethmoid can lead via its medial dural branches to hypertrophy of the anterior cranial fossa between the midline and the medial border of the cribiform plate, that is the olfactory groove. This enlarges the cribiform plate medial to the ethmoid labyrinth. The result is hypertelorism. A defect in the field borders allows for the escape of an encephalocele into the nose. The StV1 medial branch of the supratrochlear artery supplies the external frontal skin running from the midline to the medial border of the eyebrow. The skin overlying a deficiency site can atrophy while that over a zone of osseous excess may be dysplastic. The eyebrow is not involved.

The cleft process, when the medial nasopalatine is involved, affects the premaxilla in a very predictable sequence. The frontal process is always involved, even in the most trivial of clefts; this causes a deformity of the piriform fossa. At the lateral incisor zone, an external groove will appear in the alveolus. Further deficiency causes the loss of the lateral incisor. If, for any reason, the most distal aspect of the lateral nasopalatine or that of the greater palatine are affected, the back wall of the alveolus fails to develop and a full-thickness defect of the primary palate ensues. The sequence is always the same: from the incisive surface cephalad and from labial to lingual (Figures 1.25 and 1.26).

**Tessier cleft zone 2**

Zone 2 (Figure 1.24) consists of relatively simplistic oral components, the premaxilla and the internal (lingual) lamina of the alveolus housing the central and lateral incisors. These structures are supplied by the StV2 medial nasopalatine artery. The external (labial) alveolar lamina housing the medial and lateral incisors is supplied by the StV2 medial infraorbital. It also helps support the frontal process of the maxilla. Note that the internal (lingual) lamina of the alveolus housing the lateral incisor territory has an additional collateral supply from the StV2 greater palatine. This explains the great variability in nature seen in the presence or absence of the lateral incisor. On the other hand, the frontal process of the premaxilla appears to be uniquely dependent on the medial sphenopalatine. Because bone is the most distal element of the premaxilla it is the most vulnerable part of the premaxilla.

The cleft process, when the medial nasopalatine is involved, affects the premaxilla in a very predictable sequence. The frontal process is always involved, even in the most trivial of clefts; this...
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**Figure 1.26** Minimal cleft lip. Note that the forme fruste has all the features of a complete cleft: depressed nostril floor and malposition of nasalis. The greater the degree of mesenchymal deficiency, the less BMP-4 is produced. This in turn, maintains SHH in the epithelium at high levels, thus preventing fusion.

**Tessier zone 12**

Zone 12 is analogous to zone 13. It consists of intracranial and extracranial structures and extranasal structures. The intracranial part of zone 12 corresponds to the internal lamina of the frontal bone overlying the frontal sinus. The anatomy of the dural arterial supply here is uncertain but may involve contributions from the intraorbital part of the ophthalmic artery or of its branches through the anterior ethmoid. Excess tissue here can enlarge the sinus. This in turn can lead to orbital dystopia (Tessier et al., 1977).

These are all supplied by the terminal branch of the ophthalmic artery; this gives rise to two branches: the StV1 medial branch of supratrochlear artery supplies the frontal bone and the StV1 infratrochlear artery (dorsal nasal artery) supplies the lateral nasal wall. The medial supratrochlear supplies the external lamina of the frontal bone and the forehead. Excess in this zone can enlarge the frontal sinus; the glabella can be flat. Deficiencies cause cutaneous defects such as coloboma or notch in the medial 1/3 of the brow. Inferiorly, the infratrochlear axis supplies the lacrimal sac. There are two descending branches: one runs along the nasal dorsum while the other follows along the lateral nasal wall. This latter is involved in cleft zone 11. Deficiency of zone 11 shows up most commonly as a mild vertical deficiency of nasal skin. The lacrimal system is unaffected. The formation of the nostril involves induction of soft tissues by the nasal placode. When this process is interrupted, the result is either a proboscis or the outright loss of the structure altogether, a condition called hemi-nose. It is of note that the proboscis, when present, descends from the lacrimal zone. Clefts involving the infratrochlear axis are associated with absence of a recognizable lacrimal apparatus (Figure 1.27).

**Tessier cleft zone 3**

Zone 3 consists of the inferior turbinate and the corresponding lateral nasal wall, the palatal shelf, and the palatine bone. Blood supply to the lateral nasal wall comes from the StV2 lateral nasopalatine artery, including the nasal mucoperiosteum of the palatal shelf while the StV2 descending palatine artery supplies via the greater palatine artery the oral mucoperiosteum of the palatal shelf and via the lesser palatine artery the palatine bone proper (Figures 1.28 and 1.29).

Deficiency of zone 11 shows up most commonly as a mild vertical deficiency of nasal skin. The lacrimal system is unaffected. The formation of the nostril involves induction of soft tissues by the nasal placode. When this process is interrupted, the result is either a proboscis or the outright loss of the structure altogether, a condition called hemi-nose. It is of note that the proboscis, when present, descends from the lacrimal zone. Clefts involving the infratrochlear axis are associated with absence of a recognizable lacrimal apparatus (Figure 1.27).

**Tessier cleft zone 11**

This zone consists of the frontal process of the maxilla. It involves the lacrimal groove and the lacrimal segment of the medial lower eyelid. Palate clefts of zone 3 are frequently associated with zone 11 pathology. The arterial axis of zone 11 is the StV1 lateral branch of the infratrochlear artery. For this reason, zone 11 clefts destroy the lacrimal apparatus – which remains intact in other cleft zones. There is marked foreshortening of the lateral nasal skin.

**Cleft palate associated with mandibular deficiency states**

Development of the mandible is similar in plan and execution to that of the maxilla, especially when one considers the anatomy of the alveolar apparatus. In both cases, dental units based upon neural crest blastema occupy a space between two intervening membranous bone units. Running through the membranous bone is either the superior alveolar artery or the
Figure 1.27 Zones of the nose. The infratrochlear artery emerges just above the medial canthus and divides into two branches, the more medial dorsal nasal artery defines the soft tissues of the paramedian nasal dorsum, zone 12. The lateral branch supplies zone 11 and overlies the lacrimal system; it anastomoses with the angular branch of facial artery (external carotid system).

Figure 1.28 The upper turbinate is exclusively StV1 lateral nasal br. of posterior ethmoid while the middle and inferior turbinates are an interface between lateral nasal br. of anterior ethmoid and lateral nasopalatine. Knock-out of the latter axis (as in a zone 3 cleft) wipes out the entire inferior lateral nasal wall with exposure of the sinus to the oral cavity and loss of the ipsilateral palatal shelf.

Inferior alveolar artery. The external (buccolabial) lamina of the maxilla supplied by the medial and lateral branches of infraorbital artery cover respectively the incisor/canine zone and the premolar zone while the external branch of superior alveolar artery supplies the molar zone. The internal (lingual) zone is supplied by the medial nasopalatine artery to the incisors while the greater palatine artery supplies all remaining dental zones. The external (buccolabial) lamina of mandibular alveolus is supplied by, posteriorly, the mylohyoid artery and, anteriorly, the submental branch of the facial. The internal (lingual) lamina
of mandibular alveolus is supplied by the lingual artery. Thus we see a commonality of bone units supporting the dentition.

The mandible has a third zone, the ramus, which is not part of the original embryonic dentary bone. It fact, its evolutionary history is quite distinct. Not surprisingly, the ramus has an entirely different blood supply. Here we find the source of nearly all dentofacial anomalies involving the mandible. Most importantly, for our purposes, is the situation of cleft palate involving the Pierre Robin anomalad. This entity involves contributions from the first and third arches since the muscle blastema of the palate arises from somitomeres 4 and 7. Associated problems with the fourth arch have also been documented. Retropositioning of the tongue and its potential interference with bony palate shelf development is one possibility. Another possibility is that a similarity in genetic programming exists between the ramus of the mandible and the palatal shelves themselves.

**Soft palate defects: isolated vs. combined**

Diagnosis: the simplest solution is direct testing of individual muscles using a muscle stimulator such as that available from Integra Life Sciences (Figure 1.30).

Any defect affecting the StV2 components of the hard palate (horizontal palatine shelf, palatine bone) is related to the first pharyngeal arch and therefore has the potential to affect the sole muscle arising from somitomere 4: tensor veli palatini (TVP). Because this muscle relates to the cartilagenous lateral wall of the pharyngotympanic tube it is associated with opening the tube to equalize air pressure, as in swallowing and yawning. First arch pathology affecting the wall of the lateral tube and TVP may explain the relationship seen in unilateral clefts between ipsilateral muscle function and middle ear disease.

Although the developmental fields of the third pharyngeal arch do not contribute membranous bone components to the palate, the cartilagenous medial wall of the pharyngotympanic tube is a third arch derivative. Levator veli palatini arises from somitomere 7 and, when dysfunctional, diminished elevation of the soft palate can be observed. In many cases of microtia, third arch pathology is present. These patients present almost uniformly with a characteristic dampening of physiologic soft palate lift ipsilateral to the microtia.

Failure of midline fusion of the soft palate presents in a posterior-to-anterior gradient. The “cleft” is simply a mesenchymal deficiency – including a reduction in mucosal surface area, with the oral side being more affected than the nasal side. The final muscle pair to form in the soft palate is uvulus. Thus, the first manifestation of the third arch pathology is a midline notch separating these two muscles. As the defect worsens, the levator is affected and the soft palate cleft extends forward toward the posterior nasal spine. Reduction/absence of the helix seen in microtia patients is a manifestation of third arch deficiency. Such patients frequently will demonstrate levator weakness even in the absence of a cleft palate. The combination of third arch with first arch is diagnosed by dysfunction of the tensor vali palatini and/or other osseous deficiency.

Speech problems associated with velopharyngeal insufficiency and/or dysfunction in the absence of cleft palate are not infrequent. Once again, the key to diagnosis is to recognize the existence of individual muscle defects, involving partial or global deficiencies of soft palate muscle. These also include dysfunction of the superior and/or middle constrictor.

Blood supply to the soft palate involves several vessels. The lesser palatine artery from the descending palatine supplies the mucosa. The muscles of the soft palate are supplied by the ascending palatine branch of the cervical division of the facial artery. The ascending pharyngeal artery, proper to the third pharyngeal arch, can also supply the muscles of the palate.
but its primary target is the superior and inferior constrictors of the pharynx. Isolated defects in the constrictors should be part of the differential diagnosis of non-cleft velopharyngeal insufficiency.

Summary

This chapter has reviewed the developmental anatomy of the oronasopharynx. We have examined the various components that make the mesenchymal structures of the palate. The concept of fields – each with a specific neurovascular axis, each containing neural crest originating from a specific neuromere, each susceptible to failure of formation vs. disruption based upon a growth cone dysfunction – has been presented in detail.

The surgical implications of developmental fields encourage all those concerned with pediatric craniofacial anomalies to work toward a better understanding of the basic mechanisms underlying the complex problems. Surgical solutions based upon a sound embryologic basis with respect for correct field boundaries offer the best chance for the achievement of harmonious growth and correct function (Carstens, 2008c).

References


