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Chapter 66
Craniofacial Defects

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Embryology of the Primary and Secondary Palates

The neural crest plays an integral part in facial morphology. When the neural folds fuse to form the neural tube at approximately the fourth week of gestation, ectomesenchymal cells adjacent to the neural plate migrate into the underlying regions. Those in the head and face form essentially all the skeletal and connective tissues of the face: bone, cartilage, fibrous connective tissue, and all dental tissues except enamel. This transformation is effected by induction of these ectomesenchymal cells by the adjacent oral ectoderm and pharyngeal endoderm. Neural crest cells also migrate into the visceral arches, where they surround mesodermal cores.

By the end of the fourth week, the anterior neuropore has closed. What is to be the face consists of a large frontal prominence overlying the first or mandibular arch. If one manually elevates the frontal prominence, one can see into the primary mouth or stomodeum. The primary mouth is separated from the foregut by the buccopharyngeal membrane, which undergoes programmed cell death and ruptures at approximately this time in development. On both sides of the frontal prominence, the nasal placodes are forming. These bilateral structures, located just above the primitive mouth, are represented by local thickening of the surface ectoderm. Rapid proliferation of tissue known as *nasal swelling* occurs both lateral and medial to the nasal placodes. By means of selective cell death and proliferation of tissues, nasal or olfactory pits that extend into the primitive mouth are formed; they are the primitive nostrils.

Extremely active growth occurs during the fifth and sixth weeks (Fig. 66-1). The maxillary swellings, which represent the upper portion of the first pharyngeal arch, enlarge considerably

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and, by pushing the nasal swellings or prominences medially, cause them to approach each other in the midline. When the two prominences meet, the median nasal prominences and the maxillary swellings merge. Thus, the upper lip is formed laterally by the maxillary prominences and medially by the fused median nasal prominences. This development occurs near the seventh week. The lateral nasal prominences play no role in formation of the upper lip but form the alae or wings of the nose.

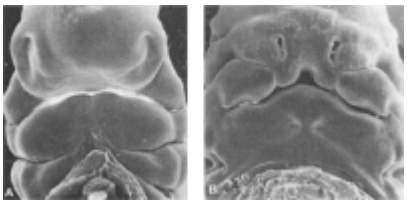


Figure 66-1. Embryology of the primary and secondary palates. Scanning electron microscopy of human embryos. **A:** Early fifth week after fertilization. **B:** Sixth week after fertilization. Median nasal process is not yet fused with maxillary process of first arch. (Courtesy of K. Sulik, Chapel Hill, NC.)

The primary palate consists of the two merged medial nasal processes that form the intermaxillary segment. The intermaxillary segment consists of two portions: a labial component that forms the philtrum of the upper lip (i.e., the indented area flanked by roughly parallel ridges that run from the columella of the nose to the middle of the upper lip) and the triangular palatal component of bone that includes the four maxillary incisor teeth. The primary palate extends posteriorly to the incisive foramen or, clinically, to the incisive papilla.

The so-called secondary palate forms at least 90% of the hard and soft palates (i.e., all except the anterior portion that holds the incisor teeth). Its development appears to be somewhat more complicated than originally was thought. The palatal shelves originate as swellings or shelflike burgeonings of the medial surfaces of the maxillary prominences. They appear in the sixth week and grow downward, lateral to and somewhat beneath the tongue. Elevation of the palatal processes to a horizontal plane is more “rigorous” anteriorly, nearer the primary palate. Elevation begins during the seventh week.

What promotes the elevation has been called *intrinsic shelf force*, but it has a complex biochemical and physiochemical basis. When the shelves are elevated to the horizontal plane, programmed cell death occurs in the overlying epithelium, permitting flow of ectomesenchyme from each side to close the gap. Complete fusion is effected by the tenth week (Fig. 66-2). In some infants, cystic degeneration of the epithelial remnants occurs, producing evanescent midline palatal microcysts.

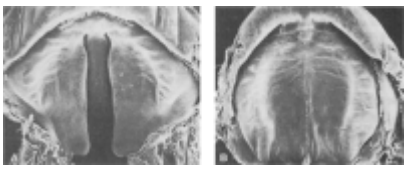


Figure 66-2. Scanning electron microscopy view of secondary palate at 8 weeks **(A)** and at 10 weeks **(B)**. (Courtesy of K. Sulik, Chapel Hill, NC.)

Cleft Lip and Cleft Palate

Epidemiology and Genetics

The degree of cleft formation varies greatly. Minimal degrees of involvement include

bifid uvula, linear lip indentations (so-called intrauterine-healed clefts), and submucous palatal cleft. Clefts may involve only the upper lip or may extend to the nostril and may be combined with defects of the hard or soft palate. Isolated palatal clefts may be limited to the uvula or they may be more extensive, cleaving the soft palate or both the soft and hard palates to just behind the incisor teeth.

A combination of cleft lip and cleft palate is more common than isolated occurrence of either. Cleft lip with cleft palate composes some 50% of the cases, with cleft lip and isolated cleft palate each constituting perhaps 25%, generally irrespective of race. Cleft lip with or without cleft palate occurs in approximately 1 per 1,000 white births (range, 0.8 to 1.6 per 1,000). Frequency is higher in Native Americans (3.5 per 1,000), Japanese (2.1 per 1,000), and Chinese (1.7 per 1,000); it is lower among blacks (0.3 per 1,000).

Isolated cleft lip may be unilateral (80%) or bilateral (20%). When unilateral, the cleft more commonly is located on the left side (approximately 70%), but it is no more extensive. Lips are cleft somewhat more frequently bilaterally (approximately 25%) when combined with cleft palate. The cleft lip and palate combination is more common in men than in women. Some 85% of cases of bilateral cleft lip and 70% of cases of unilateral cleft lip are associated with cleft palate. Cleft lip is not always complete (i.e., extending into the nostril). In approximately 10% of the cases, the cleft is associated with skin bridges or Simonart's bands.

Isolated cleft palate appears to be an entity separate from cleft lip with or without cleft palate. Numerous investigators have determined that siblings of patients with cleft lip with or without cleft palate have an increased frequency of the same anomaly but not of isolated cleft palate, and vice versa. The incidence of isolated cleft palate among both whites and blacks appears to be 1 per 2,000 to 2,500 births. It occurs somewhat more often in girls, comprising some 60% of the cases. Although a 2:1 female-to-male predilection prevails for complete clefts of the hard and soft palate, the ratio approaches 1:1 for clefts of the soft palate only.

Cleft uvula varies in degree of completeness; incomplete clefts are more common. The frequency of cleft uvula (1 in 80 white persons) is much higher than that for cleft palate with no gender predilection. The frequency in parents and siblings of probands ranges from 7% to 15%. Cleft uvula among Native American groups is high, occurring in 1 per 9 to 14 births, depending on tribal group. In blacks, it is rare. Estimates are 1 per 350 to 400 births.

Congenital pharyngeal incompetence, characterized by cleft palate speech (50%) without an overt cleft, is due to a short soft palate (60%), an imperfect muscular union across the soft palate (submucous palatal cleft), or increased depth of the nasal pharynx. Submucous palatal cleft is relatively uncommon, occurring in 1 in 1,200 children. Apparently no gender predilection is demonstrated. Some 30% of those with submucous palatal cleft have bifid uvula, with poor mobility demonstrated in 20%. A median deficiency or notch is seen in the bone at the posterior edge of the hard palate. It can be detected digitally or by a light probe placed within the nose.

Recurrence data do not suggest a simple pattern of inheritance. This finding is bolstered by twin studies indicating the relative roles played by genetic and nongenetic influences. Among twins with cleft lip with or without cleft palate, concordance is far greater in monozygotic (35.0%) than in dizygotic (4.5%) twins. In twins with isolated

cleft palate, concordance is not quite as great between the two groups (monozygotic, 26.0%; dizygotic, 5.8%). This finding suggests a stronger genetic basis for cleft lip with or

without cleft palate than for isolated cleft palate. Both cleft lip with or without cleft palate and isolated cleft palate consist of three groups: sporadic (75% to 80%), familial (10% to 15%), and syndromal (1% to 5%). Clefting is heterogeneous. Its variation and liability probably are determined by major genes, minor genes, environmental insults, and a developmental threshold.

Mechanisms of Cleft Production

By definition, cleft lip involves the failure of closure of the primary palate, and cleft palate involves failure of closure of the secondary palate. Knowledge regarding mechanisms involved in regulation of embryonic growth is sparse at best. Growth patterns can be affected also by environmental factors. A long list of teratogenic substances (e.g., corticosteroids, vitamin A, phenytoin, various folic acid antagonists) can produce clefting in rodents. Little evidence, however, suggests that any of these agents plays even a minor role in cleft palate production in humans.

Various genetic and environmental factors may inhibit the flow of neural crest cells or may affect their volume or mass so that contact between prominences is impossible or inadequate. The epithelium covering the ectomesenchyme may not undergo programmed cell death, so fusion cannot take place. Exact timing and exact positioning play critical roles.

Clefts of the primary and secondary palates occur in association in perhaps one-half of cases. A common mechanism of production has been sought. Reduction in size of both the labial maxillary prominence and the palatine process of the maxillary prominences appears to be a reasonable explanation.

Clefts of the secondary palate probably result from either hypoplasia of the shelves or delay in timing of shelf elevation. Experiments carried out on susceptible strains of mice suggest that both mechanisms are operative but at different times in gestation. Large doses of vitamin A given early in gestation inhibit palatal shelf growth and cortisone given later in gestation inhibits palatal shelf elevation.

Risk of Recurrence

In most cases, the cleft is either isolated or associated with a constellation of anomalies that do not form a recognizable syndrome. Although more than 300 cleft syndromes or associations are recognized, they constitute a low percentage of cases. Efforts must be made to recognize a cleft syndrome, because the pattern of inheritance may be simple, and the genetic risk for future affected children then may be more precise. For example, a parent with or without a cleft and paramedian pits of the lower lip has a 50% chance of having a child with cleft lip or palate.

In the case of isolated clefts, the risk to a first-degree relative of an affected individual is 2% to 4%. This information applies only to risks for similar anomalies (i.e., a parent with isolated cleft palate has no greater risk of having a child with cleft lip with or without cleft palate than anyone else, and vice versa). The risks increase as more individuals are affected. For example, if a parent and a child have clefts, the risk for a

future affected sibling increases to approximately 10% to 12%. These and other situations are presented in detail in Table 66-1.

TABLE 66-1. Facial clefts: risk of recurrence

Parents	Siblings: Normal	Siblings: Affected	Cleft lip (palate) (%)	Cleft palate (%)
Normal	0	1	4.0	3.5
	1	1	4.0	3.0
	0	2	14.0	13.0
One affected	0	0	4.0	3.5
	0	1	12.0	10.0
	1	1	10.0	9.0
	0	2	25.0	24.0
Both affected	0	0	35.0	25.0
	0	1	45.0	35.0
	1	1	40.0	35.0
	0	2	50.0	45.0

Adapted from Tolarová M. Empirical recurrence risk figures for genetic counseling of clefts. Acta Chir Plast (Praha) 1972;14:234.

The severity of a facial cleft also affects recurrence risk in the offspring. For example, researchers have found that if a parent has isolated unilateral cleft lip, the recurrence risk is 2.5%. In the presence of unilateral cleft lip *and* palate, the risk increases to 4%; and the risk is more than 5.5% for bilateral cleft lip with cleft palate.

Associated Anomalies

Cleft lip and palate often occur as isolated anomalies (i.e., thorough examinations conducted over several years have revealed no other primary abnormalities). This statement would exclude, for example, the middle-ear infections that occur so frequently secondary to cleft palate.

When data are broken down according to subtype, isolated cleft palate (20% to 50%) generally is acknowledged to be associated more often with other congenital anomalies than are either isolated cleft lip (7% to 13%) or cleft lip with cleft palate (2% to 11%). The frequency with which one or more malformations accompanies clefts of all types is almost 28%.

More malformations are found in infants with bilateral cleft lip with or without cleft palate than in those with unilateral cleft lip. The more malformations a child has, the lighter the birth weight. Congenital palatopharyngeal incompetence has been found to be associated frequently with cervical anomalies. As noted, some of these associated findings form recognizable syndromes. In 1978, 133 such disorders were listed. In 1980, an estimated 204 cleft conditions were recognized: 47 autosomal dominant, 55 autosomal recessive, six X-linked, 32 chromosomal, and 64 disorders of unknown nature associated with facial clefting. The current number of “cleft syndromes” numbers more than 300. Only the Robin malformation sequence, oculoauriculovertebral malformation, and mandibulofacial dysostosis are discussed here.

Care of the Infant with Cleft Lip or Cleft Palate

A cleft palate team—usually composed of a maxillofacial surgeon, audiologist, speech pathologist, prosthodontist, otolaryngologist, pedodontist, and geneticist—is extremely important in helping parents to understand the sequential approach to therapy for the

many attendant problems.

Feeding usually requires considerable patience. Those with more severe clefts of the lip or palate should be fed in a sitting position to minimize fluid loss through the nose. Various techniques and equipment are used to feed infants with clefts, but no single method is optimal for all infants. Infants with cleft lip or cleft palate swallow normally but suck abnormally. A cleft in the lip or palate generally does not allow sufficient negative pressure. In the case of cleft lip only, breast-feeding or an artificial nipple with a large, soft base works well. For infants with cleft lip or palate, regular breast-feeding or normal bottle feeding often is not successful because they are unable to seal either their lips or their velopharynx. With cleft of the palate only, breast-feeding or normal bottle feeding usually can be carried out if the cleft is narrow or involves only the soft palate. Soft artificial nipples with large openings are more effective.

Regular bottle nipples do not work well for infants with wider palatal clefts or the Robin malformation sequence. Enlarging the nipple opening in association with a softer nipple

with a large base and a long shaft often enables tongue movement to express a greater quantity of milk. One can also deliver milk directly into the mouth with a soft plastic bottle.

Children with cleft palate are prone to repeated infections of the middle ear and paranasal sinuses. The tonsils and adenoids enlarge, and chronic nasopharyngitis may lead to recurrent otitis media, with resultant conductive hearing loss. Nasopharyngeal infection should be treated promptly with antibiotics. The tonsils and adenoids may play a vital role in allowing normal speech. Thus, tonsillectomy and adenoidectomy, especially in those with velopharyngeal insufficiency, may result in postoperative nasal speech.

Assessing auditory function in infants with cleft palates is important and may be carried out more accurately in infants or young children by auditory specialists.

Surgical Repair of Clefts

Closure of the lip usually is carried out between the second and tenth week after birth, depending on the infant's weight and state of health. The primary purpose is to create a seal to allow normal sucking. Various techniques have been used for repair of the lip, depending on the degree and extent of defect. In those cases in which tissue in the two lip segments is insufficient to create an acceptable lip and nostril, the surgeon may have to move small flaps of tissue from other places in the upper or (occasionally) the lower lip. For bilateral cleft lip, surgery is more difficult. If the primary palate is not attached to the secondary palate, it requires repositioning. Usually, subsequent surgery is required to correct nasal alar form, to compensate for uneven growth of tissue on the two sides of the lip, or to match evenly the vermilion line on both sides. This secondary surgery is best performed during the teen years.

Surgical closure of the hard and soft palate often is performed at perhaps 18 to 24 months of age, but some surgeons prefer to wait longer. The object is to create airtight and fluid-tight closure of the cleft and to preserve the length and mobility of the soft palate, goals that often involve multiple surgical operations. If insufficient tissue is available for closure by any of the many techniques available, an obturator or speech bulb is made by the prosthodontist.

Robin Malformation Sequence

The Robin malformation sequence consists of micrognathia, glossoptosis, and cleft palate (Fig. 66-3). Some 30% of the cases represent Stickler syndrome. The mandible is small and symmetrically receded. Congenital murmurs or heart anomalies (e.g., ventricular septal defect, atrial septal defect, patent ductus arteriosus) have been observed in 15% to 20% of those who have died in early infancy. Esotropia and congenital glaucoma are relatively common. Approximately 20% exhibit severe mental retardation, but whether this condition is primary or secondary to asphyxia is not known. The palatal defect may vary widely from cleft uvula to clefting that involves two-thirds of the hard palate and is horseshoe shaped. The small mandible often achieves catch-up growth by 4 to 6 years of age, but the angle always is somewhat abnormal. Difficulty in the inspiratory phase of respiration is apparent, with periodic cyanotic attacks, labored breathing, and recession of the sternum and ribs, especially apparent when the child is supine. The respiratory difficulty usually is evident at birth, but it may not be severe for the first week. Immediate airway maintenance is critical. In mild cases, it may be accomplished by keeping the individual prone with the head suspended by a pulley in a stockinette cap. In more severe cases, the tongue tip may be sutured temporarily to the lower lip or anterior mandible. Tracheotomy rarely is required.

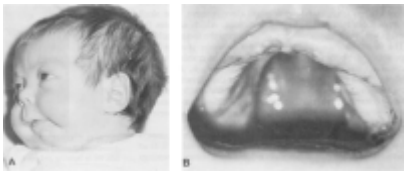


Figure 66-3. Robin malformation sequece. **A:** Small retruded lower jaw. **B:** U-shaped palatal cleft.

Oculoauriculovertebral Malformation

Facial asymmetry due to hypoplasia or displacement of the pinna is common in oculoauriculovertebral malformation (hemifacial microsomia, Goldenhar syndrome; Fig. 66-4). The maxillary, temporal, and malar bones on the involved side are reduced in size and flattened, and the ipsilateral eye is set low. Bilateral involvement occurs in approximately 10% of cases. Malformation of the external ear varies from complete aplasia to a crumpled, distorted pinna displaced anteriorly and inferiorly. Supernumerary ear tags may occur anywhere from the tragus to the angle of the mouth. When epibulbar dermoids are present, ear tags tend to be bilateral. Conductive hearing loss, due to middle-ear abnormalities or absence or deficiency of the external auditory meatus and canal, is found in 40% of cases. Epibulbar dermoid varies: white to yellow, flattened, ellipsoid, solid, and usually located in the lower, outer quadrant at the limbus. Coloboma of the upper lateral eyelid is common in patients with epibulbar dermoids.

When unilateral microphthalmia or anophthalmia is present, mental retardation is increased. Approximately 5% of cases have cleft lip or palate. Radiographically, vertebral anomalies found in some 50% of cases include complete or partial synostosis of two or more vertebrae and hemivertebrae. Aplasia or hypoplasia of the mandibular ramus is seen on the ipsilateral side. A small percentage of cases have agenesis of one lung and various renal anomalies (e.g., absent kidney, double ureter). The frequency of the condition is approximately 1 in 3,000 live births. Almost all

cases appear to have multifactorial inheritance, with a recurrence risk of approximately 1%. However, in a few families, the disorder appears to be autosomal dominant.

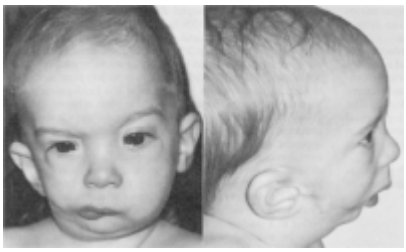


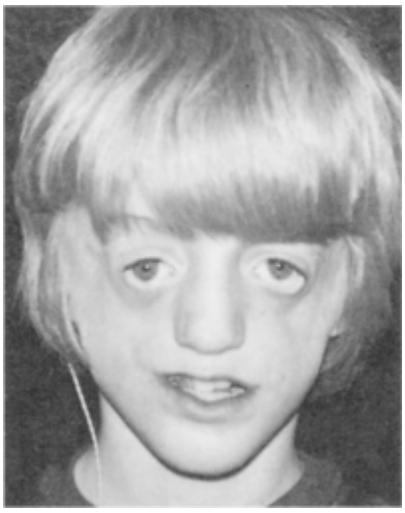
Figure 66-4. Oculoauriculovertebral malformation. Note hemifacial microsomia, repaired macrostomia, and low-set, somewhat dysmorphic pinna. Ear tags have been removed. (Courtesy of M. M. Cohen Jr., Halifax, Nova Scotia, Canada.)

Surgical correction ranges from lengthening the mandible to construction of a new temporomandibular joint and ramus with rib grafts and costochondral junction.

Mandibulofacial Dysostosis

Mandibulofacial dysostosis, or Treacher Collins syndrome, is characterized by downward-slanting palpebral fissures and coloboma of the outer third of the lower lid with deficient cilia medial to the coloboma (Fig. 66-5). The nose appears large because of lack of malar development. A nasofrontal angle commonly is obliterated. Micrognathia is a constant feature. Cleft palate is found in 30%. The external ear frequently is deformed, crumpled forward, or misplaced, with some patients having absence of the external auditory canal or an ossicular defect with conductive hearing loss. Extra ear tags and blind fistulas may be found between the tragus and angle of the mouth. Radiographs show defects in the zygomatic arches. The undersurface of the body of the mandible is markedly concave. The syndrome has autosomal dominant inheritance, with high penetrance and markedly variable expressivity. The gene has been mapped to 5q31.3–q33.3, and prenatal diagnosis is possible.

Figure 66-5. Mandibulofacial dysostosis. Boy with malar hypoplasia with downward-slanting palpebral fissures. Colobomas of outer third of lower lids. Note hearing aid cord.



Embryology of Craniofacial Skeleton

Understanding the craniosynostoses and their syndromes requires an understanding of skull development. The skull forms from two parts: the neurocranium, which encases the brain, and the viscerocranium, which forms the facial skeleton. The neurocranium consists of a membranous portion composed of flat bones that form the calvaria, or cranial vault. A cartilaginous component, the chondrocranium, forms the bones of the skull base. The flat bones of the calvaria develop by membranous ossification. Several primary ossification centers, consisting of needlelike bone spicules, progressively enlarge and radiate peripherally, forming the frontal, parietal, and occipital bones.

In the newborn, the flat bones of the calvaria are separated by sutures (i.e., narrow bands of connective tissue). Points at which more than two bones meet exhibit wide sutural openings known as *fontanelles*. The largest of these is the anterior fontanelle, at the meeting of the two parietal bones and two frontal bones. The posterior fontanelle is situated at the junction between the two parietal bones and the occipital bone. A third fontanelle occasionally is present in the sagittal suture some 1 cm anterior to the posterior fontanelle. Two other embryonal fontanelles are found: the anterolateral (or sphenoidal) fontanelle and the posterolateral (or mastoid) fontanelle. The sutures and fontanelles permit skull bones to overlap during passage of the head through the vaginal canal. After birth, the bones resume their position. The anterior fontanelle usually is clinically closed by 13 months of age (range, 7 to 19 months). The posterior fontanelle, usually clinically inapparent at birth, closes anatomically at approximately 3 months of age. The sutures and fontanelles remain membranous to allow growth of the cranial vault in response to expansion of the brain. Many sutures remain open until adult life. In contrast to the membranous neurocranium, the base of the skull (or chondrocranium) initially consists of several cartilages that fuse and undergo endochondral ossification.

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The viscerocranium or facial skeleton is formed mainly from the cartilages of the first two pharyngeal arches. The first pharyngeal arch is divided into a dorsal maxillary process and a ventral mandibular process. The former gives rise to the maxilla, the zygomatic bone, and part of the temporal bone. The cartilage of the first pharyngeal

arch is known as *Meckel's cartilage*. The ectomesenchyme surrounding the cartilage condenses and ossifies, giving rise to the mandible by membranous ossification. Meckel's cartilage actually acts only as a template, except for its most dorsal portion, which gives rise to the malleus and incus. Remnants may be found in the sphenomandibular ligament.

Craniosynostosis

Obliteration of sutures that takes place before or soon after birth inhibits the growth of adjacent bones perpendicular to the course of the obliterated suture. Consequently, skull diameter is reduced in this direction. Compensatory and abnormal growth, however, proceeds in directions permitted by open sutures and fontanelles (Fig. 66-6). If a single suture is involved, it is termed *simple craniosynostosis*; if multiple sutures are involved, it is called *compound craniosynostosis*. Early obliteration of the sagittal suture results in *scaphocephaly* (*dolichocephaly*; Fig. 66-7). The skull is long and narrow, and the parietal protuberances are absent. As the brain expands, the coronal and lambdoidal sutures are widened, and frontooccipital elongation takes place. In some cases, a bony crest is seen in place of the sagittal suture. In *brachycephaly*, the coronal sutures are fused prematurely, resulting in a short, square-appearing cranial configuration (Fig. 66-8). *Plagiocephaly* refers to skewing of the skull due to premature unilateral fusion of a coronal or lambdoidal suture. *Trigonocephaly* describes a keel-shaped forehead due to premature fusion of the metopic suture. *Acrocephaly* (*turricephaly*) results from multiple suture closures. The highest point on the calvaria usually is near the anterior fontanelle, head form being short, high, and broad. Chiefly, the coronal suture is affected, although the sagittal and lambdoid sutures frequently are involved. If the anterior fontanelle and metopic suture remain open, the skull expands in abnormal directions, resulting in steep frontal, parietal, and occipital bones and a high, broad, short skull. Often, digital impressions are evident.

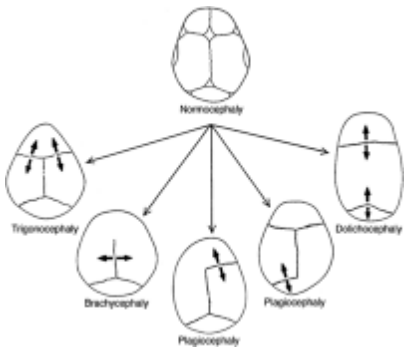
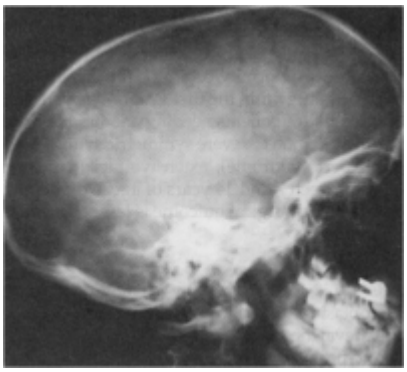


Figure 66-6. Craniosynostosis. Various skull shapes resulting from premature fusion of individual sutures or groups of sutures. (Courtesy of M. M. Cohen, Jr., Halifax, Nova Scotia, Canada.)

Figure 66-7. Scaphocephaly (dolichocephaly).



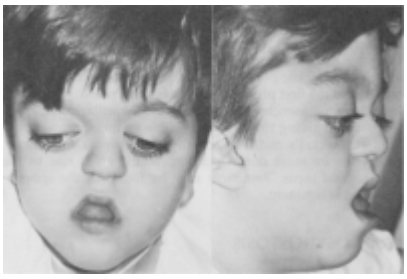


Figure 66-8. Brachycephaly.

Craniosynostosis may be primary, as in simple or compound premature fusion described earlier, or it may be secondary to a known disorder (e.g., thalassemia, hyperthyroidism, microcephaly, mucopolysaccharidoses, rickets). Little is known about pathogenesis. Transforming growth factor–beta (types 1, 2, and 3), insulinlike growth factor–1, and some fibroblast growth factors and receptors (1, 2, and 3) are expressed at the osteogenic fronts of developing calvarial sutures and play a role in early pathologic closure (i.e., craniosynostosis).

Finally, craniosynostosis may be isolated or syndromic. In 1993, Cohen listed 90 syndromes of craniosynostosis (monogenic, 40; chromosomal, 16; environmentally induced, four; unknown genesis, 24; miscellaneous, six). A few more common syndromes are discussed in this chapter: Crouzon disease, Apert syndrome, Saethre-Chotzen syndrome, Pfeiffer syndrome, and Carpenter syndrome.

Epidemiology and Genetics

The frequency of simple or nonsyndromal craniosynostosis is approximately 0.34 to 0.40 per 1,000 newborns. Racial predilection is not apparent. Premature fusion of the sagittal suture is the most common type of simple synostosis, constituting approximately 55% of cases. The male-to-female gender predilection is 3:1. Unilateral or bilateral coronal synostosis comprises approximately 20% to 25% of cases, with a slight predilection for female infants. Metopic synostosis and lambdoidal synostosis each constitute a few percent. Involvement of two or more sutures comprises 15%.

Simple craniosynostosis usually is sporadic. Of patients with coronal synostosis, some 10% are familial; of patients with sagittal synostosis, some 2% are familial. Among those with familial occurrence, mutations in both fibroblast growth factor receptors 2 and 3 have been demonstrated. In some kindreds, the same suture is subject to synostosis in affected individuals and, in others, different sutures are fused. Sagittal synostosis appears to be most consistent with multifactorial inheritance, the frequency in the general population being approximately 1 in 4,200, with a recurrence risk of approximately 1 in 64 siblings. Twin studies clearly indicated that single-gene inheritance does not play a large role in craniosynostosis because discordance is more frequent than is concordance in monozygotic twins.

Treatment in Infancy

Treatment of craniosynostosis in infancy is controversial. The craniosynostoses represent not only diverse groups; extreme variables are found within each group. Opinions regarding treatment vary from conservative observation until completion of facial growth to radical extensive surgical correction in the first months of life. Such complications as increasing intracranial pressure or progressive corneal exposure secondary to exorbitism often mandate early treatment.

Patients with premature closure of cranial sutures should be treated surgically when younger than age 2 years, as should those patients with metopic suture closure younger than 6 months old. The operation performed most frequently for simple craniosynostosis is linear craniectomy parallel to the prematurely fused suture. Polyethylene film is inserted over the bony margins to delay secondary closure. Bilateral, premature closure of the coronal sutures frequently is accompanied by anomalies of the facial, orbital, and sphenoid bones, with downward displacement of the orbital roof and overgrowth of the lesser wing of the sphenoid, the orbits being markedly reduced in size, thus causing exophthalmos. Maximum decompression of the cranial vault rather than orbital decompression is carried out. Canthorrhaphy is performed to avoid dryness of the cornea and prolapse of the globe. Complex plastic surgical treatment of severe facial deformities of craniofacial dysostoses has been described in detail by Tessier. The optimal time for such operations is from 10 to 12 years of age.

Excellent results can be obtained from treating asymmetric synostosis at younger than 1 year of age by unilateral orbital repositioning and forehead remodeling. No further surgery is needed in more than 90% of patients. For bilateral or symmetric synostoses and mild upper-face deformity, orbital advancement and forehead reshaping carried out within the first year of life were less satisfactory, with some 50% of patients needing another major osteotomy. For those with moderate to severe symmetric synostoses (Crouzon disease and Apert syndrome), extensive facial reconstruction is performed at between 7 and 14 years of age. Despite delayed and aggressive treatment, surgical outcome is less satisfactory.

Crouzon Disease

Crouzon disease is characterized by premature craniosynostosis, midface hypoplasia with shallow orbits, and ocular proptosis (Fig. 66-9). Birth prevalence is approximately 16 per 1,000,000 births. Premature and progressive craniosynostosis usually begins during the first year of life and usually is complete by 2 or 3 years of age.

Approximately 30% of patients complain of headache; seizures have been documented in 10%. The hypoplasia of the midface is associated with relative mandibular prognathism, drooping of the lower lip, and short upper lip. Often, the nasal bridge is flat, and the nasal tip may appear beaklike. Narrow, high-arched palate due to lateral palatal swellings, crowding of upper teeth due to hypoplastic maxilla, and open bite are characteristic. Some 35% of patients are obligate mouth breathers. Cleft palate is observed in approximately 30%, and bifid uvula is seen in 10% of cases.

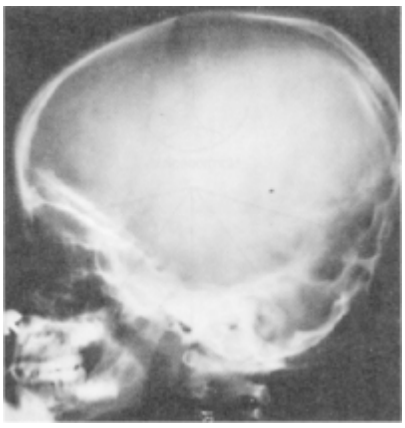


Figure 66-9. Crouzon disease. Downward-slanting palpebral fissures, facial asymmetry, hypoplastic midface, exorbitism, relative mandibular prognathism. (Courtesy of M. M. Cohen Jr., Halifax, Nova Scotia, Canada.)

Exophthalmos, secondary to shallow orbits, is a constant finding. Exotropia (75%), exposure conjunctivitis (50%) or keratitis (10%), poor vision (45%), optic atrophy (25%), hypertelorism, and nystagmus are noted. Rarely, spontaneous luxation of the globes occurs. Atretic auditory canals (15%) and malformed ossicles are associated with conductive hearing loss in more than 50% of patients. Stiffness of joints, especially the elbows, has been reported in approximately 15%. Head circumference and body height generally are smaller than normal.

Radiographically, the coronal and sagittal sutures nearly always are fused, the lambdoidal in 80% of patients. Other findings include digital markings (90%), calcification of stylohyoid ligament (85%), deviation of nasal septum (35%), obstruction of nasal pharynx (30%), and cervical spine anomalies (30%). Cephalometric studies have shown the calvaria to be short, the forehead steep, the occiput flattened, and the cranial base shortened and narrowed, with the clivus especially abbreviated. Inheritance is autosomal dominant, with sporadic cases constituting approximately 50% of cases.

Crouzon disease is due to a mutation in fibroblast growth factor receptor 2 on chromosome 10q25–q26. Many mutation sites have been documented in the third immunoglobulin domain. Crouzon disease with acanthosis nigricans maps to fibroblast growth factor receptor 3 at 4p16.3.

Apert Syndrome

Apert syndrome is characterized by congenital craniosynostosis leading to turribrachycephaly, syndactyly of hands and feet, various ankyloses, and progressive synostoses of the hands, feet, and cervical spine (Figs. 66-10 and 66-11). Most patients are mentally retarded. Approximately 25% have pigment dilution of the hair. Facial variability is marked; the orbits are markedly hyperteloric, with the midface usually

underdeveloped, lending prominence to the mandible. The skull is malformed, with the frontal and occipital bones flattened and the apex of the cranium located near or anterior to the bregma. Cleft of the soft palate has

been observed in approximately 35% of cases. Malocclusion is common because of midface hypoplasia. The hands and feet are deformed symmetrically. A middigital hand mass with bony and soft tissue syndactyly of digits 2, 3, and 4 often is found. Often, digits 1 and 5 are attached completely to the middigital hand mass. Frequently, the hallux is separated partially from the rest of the toes, which have complete soft tissue syndactyly and often a common nail. Six metatarsals have been noted in several cases. The upper extremities are shortened, and ankylosis is possible in joints, especially those of the elbow, shoulder, and hip. Acne vulgaris is noted commonly, with extension to the forearms. Apert syndrome occurs in approximately 16 of 1,000,000 births. Inheritance is autosomal dominant, but the number of cases of transmission from parent to child is few because of the mental retardation and physical appearance. The syndrome is due to mutations in the fibroblast growth factor receptor 2 at 10q25–q26, and the mutations are exclusively of paternal origin.

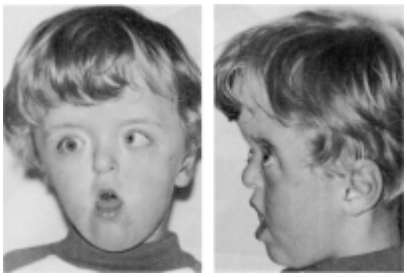


Figure 66-10. Apert syndrome. Frontal bossing, brachycephaly, hypertelorism, strabismus, exorbitism, depressed midface. (Courtesy of M. M. Cohen Jr., Halifax, Nova Scotia, Canada.)

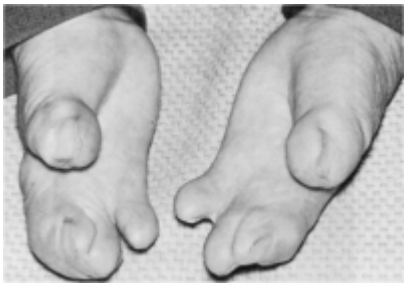


Figure 66-11. Apert syndrome. Extensive soft tissue syndactyly of hands. Note middigital hand mass composed of digits 2 to 4 and separate thumb and little finger. (Courtesy of L. Bergstrom, Los Angeles, CA.)

Pfeiffer Syndrome

Pfeiffer syndrome consists of craniosynostosis resulting in turribrachycephaly. Broad

thumbs and great toes and partial soft tissue syndactyly of the hands and feet are common. Autosomal dominant inheritance is evident, with complete penetrance and variable expressivity. Pfeiffer syndrome has been shown to be heterogeneous. Pfeiffer syndrome can be divided into three types: type 1 is the classic type, type 2 (constituting approximately 5%) has cloverleaf skull and elbow fusion, and type 3 is similar to type 2 but does not have cloverleaf skull. Various visceral malformations are found in type 3. Both types 2 and 3 are sporadic. The infants usually die within the first few weeks of life.

Most examples map to 10q25–q26 at fibroblast growth factor receptor 2 (*FGFR2*) and, less often, to 8p11.2–p12 (*FGFR1*). Those with cloverleaf skull map to *FGFR2*, whereas those with the milder form generally map to *FGFR1*.

Craniosynostosis, especially involving the coronal suture, results in turribrachycephaly. Increased digital markings may be observed with age. Maxillary hypoplasia, shallow orbits, and depressed nasal bridge also are seen. Orbital hypertelorism, down-slanting palpebral fissures, proptosis, and strabismus have been reported (Fig. 66-12). Intelligence usually is normal, but severe retardation and various central nervous system defects are observed in survivors of the cloverleaf-skull anomaly.

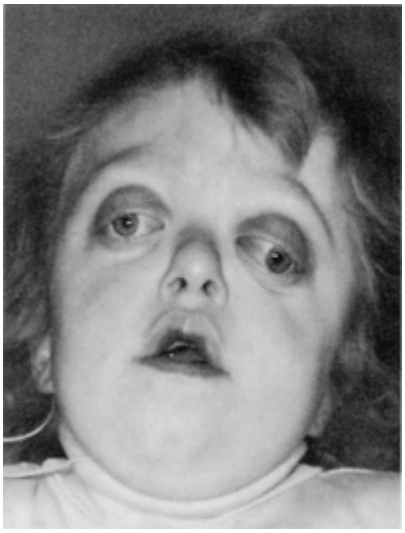


Figure 66-12. Pfeiffer syndrome. Exorbitism, downward-slanting palpebral fissures. Note hearing aid cord.

The thumbs and great toes are broad, usually with varus deformity (Figs. 66-13 and 66-14). Mild soft tissue syndactyly predominantly involves the second and third digits. Occasionally,

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middle phalanges are absent. The proximal phalanges of both thumbs are trapezoidal but may be triangular. Pollux varus commonly is found. The proximal phalanges of both great toes are trapezoidal, and hallux varus is common. The first metatarsals are broad, with partial reduplication in some cases. Symphalangism of both hands and feet has been reported. Fusion of carpals, tarsals, and the proximal ends of the metatarsals has been noted. Radiohumeral and radioulnar synostoses have been described in types 2 and 3.

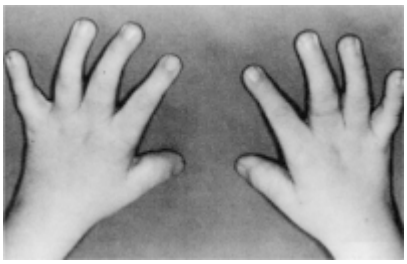


Figure 66-13. Wide thumbs of Pfeiffer syndrome.

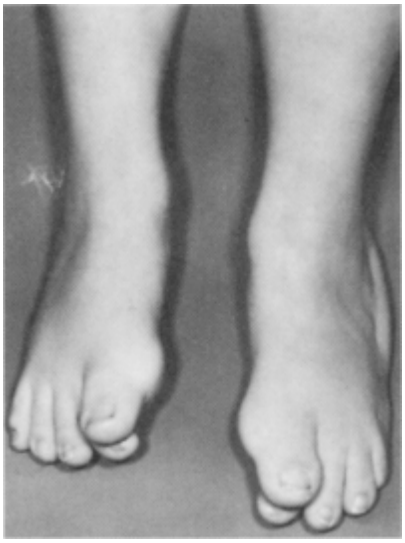
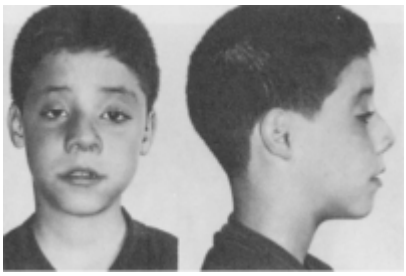


Figure 66-14. Wide halluces of Pfeiffer syndrome.

Saethre-Chotzen Syndrome

Asymmetric craniosynostosis produces plagiocephaly and facial asymmetry (Fig. 66-15). Acrocephaly and (occasionally) scaphocephaly have been noted. Head circumference frequently is reduced, and often the frontal hairline is low. Strabismus, myopia, hyperopia, ptosis, and hypertelorism are frequent. The ears may be dysplastic, with folded helices, prominent antihelices, and posterior rotation. Some degree of hearing loss is common. The nose tends to be beaked, with deviation of the nasal septum, and the nasofrontal angle is flattened. Occasional partial cutaneous syndactyly is evident in the second and third fingers. Intelligence usually is normal, but mild to moderate mental retardation has been found occasionally. Inheritance is autosomal dominant, with complete penetrance and variable expressivity. The gene has been mapped to chromosome 7p21.2. Roentgenography usually reveals coronal synostosis, reduced length of posterior cranial base, low position of the sella turcica, reduced facial depth, steep mandibular plane angle, and absence or reduced size of paranasal sinuses.

Figure 66-15. Saethre-Chotzen syndrome. Note facial asymmetry and ptosis of eyelid.



Carpenter Syndrome

Carpenter syndrome consists of acrocephaly, soft tissue syndactyly (especially involving the third and fourth fingers), brachymesophalangy, preaxial polydactyly and syndactyly of the toes, coxa valga and pes varus, congenital heart disease, mental retardation, hypogenitalism, mild obesity, and hernia. The syndrome has autosomal recessive inheritance.

Height usually is in the low 25% range of normal, but weight often is above average. The obesity mainly involves the trunk, proximal limbs, face, and nape. Usually, the skull is tower-shaped. Although premature fusion may involve all cranial sutures, synostosis often is asymmetric, producing a distorted calvaria, in some cases with cloverleaf skull (Figs. 66-16 and 66-17). On radiography, the sagittal and lambdoidal sutures often are observed to fuse first, the coronals being the last to close.

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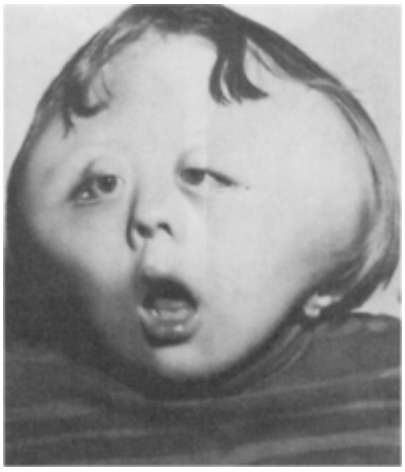
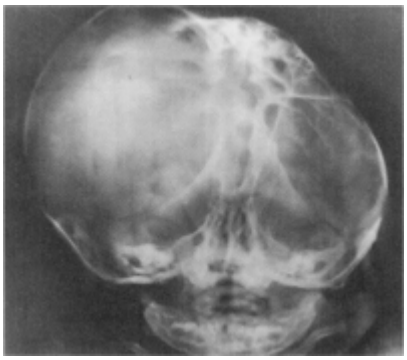


Figure 66-16. Carpenter syndrome. Downward-slanting palpebral fissures, hypertelorism, cloverleaf skull.

Figure 66-17. Asymmetric cloverleaf skull of Carpenter syndrome. (Courtesy of H. Schönenberg, Aachen, Germany.)



The hands are short, and the fingers are somewhat stubby, with a simple flexion crease (Fig. 66-18). Soft tissue syndactyly often occurs between the third and fourth fingers, with less pronounced syndactyly between other fingers. Radiography reveals brachymesophalangy of all digits or agenesis of some middle phalanges of the second to fifth digits. Usually present are bilateral varus deformities of the feet and preaxial polydactyly, with duplication of the first or second toe. The toes usually exhibit soft tissue syndactyly. Metatarsus varus and replication of the second toe are frequent. The first metatarsal is short and remarkably broad, with only two phalanges present in each toe. In nearly all cases, genu valgum has occurred, with lateral displacement of the patellae. Congenital heart disease of various types (e.g., ventricular septal defect, atrial septal defect, patent ductus arteriosus, pulmonary stenosis, tetralogy of Fallot) have been reported. Most patients are mildly retarded, but some have normal intelligence.

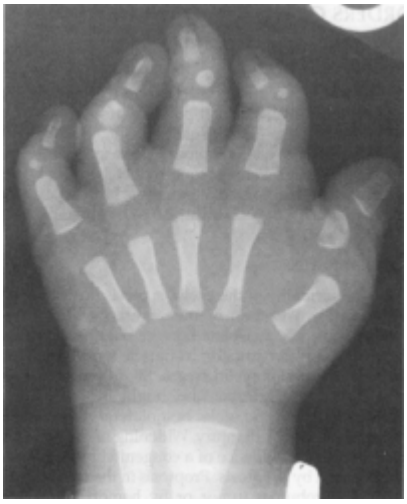


Figure 66-18. Hypoplasia of middle phalanges in Carpenter syndrome. (Courtesy of A. Poznanski, Chicago, IL.)

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