Converse: Chapter 46

Rare Craniofacial Clefts

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The cry of a newborn lingers forever when its face is marred by a rare craniofacial cleft. The audible cry is perpetuated as an inner silent one as the child begins to perceive his misfortune and goes through life being the subject of the crude, curious stares of society.

Craniofacial clefts exist in a multitude of patterns, varying in degrees of severity. Although extreme distortions initially appear to be bizarre and defy description, most craniofacial clefts occur along predictable embryologic lines. They can be unilateral or bilateral. In addition, clefts of different types can exist on opposite sides of the face of an affected individual.

Incidence

The exact incidence of rare craniofacial clefts is not known, and estimates vary widely. This is to be expected, since the cases are rare and the methods of data collection are not standardized. Extensive reviews of congenital malformation by Murphy (1938), Stevenson, Worcester, and Rice (1950), and Ivy (1957) do not categorize facial clefts into specific types.

A general idea of the magnitude of the problem can be drawn from studies of the occurrence of the common clefts of the lip and palate (Davis (1935) found four median clefts of the lip and five oblique facial clefts in a series of 937 examples of common clefts of the lip and palate. Blackfield and Wilde (1950) noted only five lateral (transverse) facial clefts during a period in which they observed 500 clefts of the lip. Burian (1957) reported 97 cases of rare facial clefts in a series of nearly 4000 consecutive common clefts of the lip accumulated over a 40-year period. Fogh-Andersen (1965) detected 48 examples of rare craniofacial clefts among 3988 consecutive cases of facial clefts gathered over a 30-year period. of the 48 rare clefts, there were 15 median clefts of the lip, 3 oblique facial clefts, 12 transverse facial clefts, 3 atypical cleft palates, 8 clefts of the nose, and 7 clefts of the scalp. Popescu (1968) reported 14 transverse facial clefts in a series of 1475 patients. Pitanguy (1968) collected 25 patients with rare facial clefts in a group of 736 patients with common clefts. Based on these reports, the occurrence rate of rare craniofacial clefts as compared to common clefts would range between 9.5:1000 and 34:1000. The true incidence is certainly higher, since some of the reports included only one type of cleft.

Birth certificate reviews have also been used in an attempt to define the incidence of facial anomalies (Ivy, 1957, 1963; Conway and Wagner, 1965). Ivy, however, has cited several inherent problems in the use of birth certificates to search for even the common anomalies. Birth certificate reviews are plagued by a lack of standardized nomenclature, the possibilities of an incorrect diagnosis by the clinician, the potential misinterpretation by the reviewer of the reported conditions, and the listing of multiple birth anomalies in the same child. Furthermore, birth certificates record only malformations occurring in live births.
It has been documented that the intrauterine incidence of facial deformities is higher than that found at birth. Hertig, Rock, and Adams (1956) found that 40 per cent of the fertilized ova examined during the first 17 days after conception were abnormal; the vast majority of abnormal oval terminate in spontaneous abortion. Warburton and Frazer (1956) showed that a high frequency of malformations exists in spontaneously aborted and stillborn fetuses. Nishimura (1969) studied material gathered from therapeutic abortions in an attempt to eliminate the built-in sampling bias of studies based on spontaneous aborted and stillborn fetuses. When 13,840 specimens between the ages of 3 and 18 weeks were examined, nearly 5 per cent had some form of external anomaly. Craniofacial malformations of all types were observed at the rate of 42.5 per 1000.

The possibility exists that more craniofacial clefts will be seen in the future. This speculation is raised since the common clefts of the lip and palate appear to be increasing in frequency (Gylling and Soivio, 1962; Fogh-Andersen, 1965; Moller, 1965; Tünte, 1969).

**Embryologic Aspects of Rare Craniofacial Clefts**

An understanding of the normal events of the embryonic development of the face facilitates the study of rare craniofacial clefts. A detailed discussion of the normal embryology is presented in Chapter 53. A brief summary of the pertinent events follows.

The embryologic development of the face takes place between the fourth and eighth weeks of gestation (Patten, 1968). The midportion of the face develops immediately anterior to the forebrain by differentiation of the broad midline frontal nasal prominence. Thickened ectodermal plates, the nasal placodes, arise from either side of the frontal nasal prominence just above the stomodeum. Progressive elevation of the mesoderm at the margins of the placodes produces a horseshoe-shaped ridge which is open inferiorly. The limbs of the placode become the medial and lateral nasal processes. The paired medial nasal processes merge with the frontonasal prominence to form the major portion of the frontal process. The medial nasal processes gradually enlarge to displace the frontonasal prominence in a cephalic direction. The medial nasal processes coalesce in the midline during the sixth week. Their caudal prolongations, the globular processes, follow a similar pattern as they expand above the midportion of the stomodeum. The premaxilla, the midportion or philtrum of the upper lip, the columella, the nasal tip, the cartilaginous portion of the nasal septum, and the primary palate are derived from the paired medial element. Above them the frontonasal process persists and narrows to form the bridge and root of the nose. The lateral nasal processes form the alar region of the nose.

The mandibular arch lies between the stomodeum and the first branchial groove, marking the caudal limits of the face. Its paired, free ends enlarge and converge ventrally to complete the continuity of the arch during the sixth week. The lower lip and mandible are developed from the mandibular arch. Paired lateral elevations of the pharyngeal surface of this arch unite in the midline to form the anterior portion of the tongue. During the sixth week three hillocks appear on the caudal border of the first branchial arch (His, 1885). On the cephalic border of the second (hyoid) arch, three corresponding hillocks can also be identified. The external ear is formed from these elevations. The tragus and the crus of the helix are derived from the first arch, as are the incus and malleus of the middle ear. The second arch contributes the remainder of the external ear and the stapes of the middle ear.
Budding off the mandibular arch are paired postocular masses of paraxial mesoderm which constitute the maxillary processes. These triangular mesodermal masses progressively enlarge toward the ventral surface. A deep groove, the naso-optic furrow, marks the superomedial margin of the maxilla from the developing eye and the lateral nasal process. The inferior border of the maxilla separates from the mandibular arch. The maxillary process ultimately coalesces with the mesoderm of the globular processes to form the upper lip. The cheek, maxilla, zygoma, and secondary palate are also derived from the maxillary processes.

The relationship of the various embryologic processes to the adult face is shown in the figure.

As can be seen, the embryopathogenesis of the craniofacial region is extremely complex. During a short four-week period, an extreme demand is placed upon the coordination of cell separation, migration, and interaction. The proper amount of tissue must be present at an exact time in the correct three-dimensional relationship. Precise movement and timing are critical. Any mishap in this intricate program can lead to disastrous consequences. The chasm that is produced usually falls along predictable embryonic lines. Some clefts, however, are found in atypical locations that do not correspond to the normal lines of union of the facial processes. Various theories have been proposed to explain the formation of clefts.

**Theories of Facial Cleft Formation.** Two leading theories of facial cleft formation exist. The "classic" theory, proposed by Dursy (1869) and His (1892), states that the failure of fusion of the facial processes is responsible for the development of clefts. This concept was questioned by Pohlmann (1910) and Veau and Politzer (1936) as the theory of mesodermal migration and penetration began to emerge; the investigations of Stark (1954) supported this challenge.

Although most of the present knowledge is based on the study of cleft lip and palate morphogenesis in nonhuman embryos, it is highly probable that rare craniofacial clefts are produced by similar mechanisms.

The classic concept of fusion pictures the central region of the face as the site of union of the free ends of the facial processes. The face begins to take form as the various processes fuse. Thus, as an example, the upper lip is formed by the union of the fingerlike ends of the maxillary processes as they meet and coalesce with the paired globular processes beneath the nasal pits. Once epithelial contact is established, penetration by the mesoderm occurs to complete the fusion and the formation of the upper lip and primary palate. Disruption of this sequence leads to the formation of a cleft.

Proponents of the mesodermal penetration theory feel that the free end facial processes do not exist. Warbrick (1938) and Stark and Ehrmann (1958) have shown that separate processes as such are not found in the central portion of the face. According to their work (see Chapter 39), the central portion of the face is composed of a continuous sheet of a bilamellar membrane of ectoderm known as the primary plate. The bilamellar membrane of ectoderm is demarcated with epithelial seams which delineate the principal "processes". Into this double layer of ectoderm, called "the epithelial wall" (Hochstetter, 1953), mesenchyme migrates and penetrates to smooth out the seams. Caudal to the stomodeum, the lower face
and neck are formed by a series of branchial arches. At first three arches consist of a thin sheet of mesoderm lying between the ectoderm and endoderm. The craniofacial mesoderm is then augmented by neuroectoderm brought in by the migrating neural crest cells.

The importance of the neural crest cells was first recognized by Johnston (1965). The cells arise from the dorsolateral surface of the neural tube and migrate beneath the ectoderm to form a continuous layer that supplements the underlying mesoderm of the frontonasal process and the branchial arches. The facial skeleton is believed to be principally derived from neural crest cells. If penetration by the neuroectoderm does not occur, the unsupported epithelial wall breaks down to form a facial cleft. The severity of the cleft is inversely proportional to the degree of penetration by the neuroectoderm. If penetration fails altogether, a complete cleft is formed as the epithelial wall dehisces; partial penetration leads to the development of an incomplete cleft.

Hoepke and Maurer (1939) borrowed from each of the two leading theories. They suggested that failure of fusion is responsible for facial cleft formation, and they regarded the penetration of the mesoderm as an attempt by the embryo to bridge the gap and, thus, heal the imperfection. The severity of the cleft would depend upon the success of the secondary healing effort.

Many voids remain in the complete understanding of the formation of facial clefts. It is generally agreed that clefts of the palate are formed by the failure of fusion. It is principally in the pathogenesis of the cleft lip that complete accord is absent. The role of the proposed schemata in the formation of rare craniofacial clefts is not precisely defined. Nevertheless, the concepts of fusion and mesodermal penetration enable one to understand the problems of unusual clefts.

Clefts of Midline Craniofacial Structures. The most minor example of a midline facial cleft is that of the median cleft of the upper lip. This lip irregularity can be explained by the imperfect union of the paired globular processes. Increased disruption in the process could lead to the formation of a bifid frenulum, a midline notch of the alveolus, a midline cleft of the palate, or a bifid nose. Frontonasal dysplasia and a median frontal encephalocele with orbital hypertelorism are examples of major midline developmental failures. Disfigurement of this magnitude occurs when the frontonasal prominence remains in its embryonic location. The forebrain thus retains its low overlying position and interferes with the normal converging movement of the optic placodes toward the midline. Hence, the eyes remain arrested in their "lateralized" hypertelorico embryonic setting.

At the other end of the spectrum, morphokinetic arrest of the frontonasal prominence can produce monstrous hyperteloric malformation, such as cyclopia, ethmocephaly, and cebocephaly (see also Chapter 56. The mildest expression of this type of developmental arrest is characterized by the absence of the philtral region of the lip (false median cleft lip) and agenesis of the primary palate. Cohen and his associates (1971a) suggested that the basic faulty mechanism producing these abnormalities lies in the flawed interaction between the notochordal plate and the neuroectoderm of the brain plate and the oral plate. The notochordal plate in the embryo begins just caudal to the optic plates. When the notochordal plate is abnormally short and its cephalic end is caudally displaced, development of the neuroectoderm and frontonasal process is inhibited. Hypotelorism is produced because of the
failure of the optic anlagen to move in a lateral direction. Because of the intimate association of the frontonasal prominence with the development of the forebrain, the severity of the craniofacial malformation appears to parallel that of the forebrain (DeMyer and Zeman, 1963; Yakovlev, 1956). The extent of external facial disorganization, therefore, provides a clue to the severity of the developmental arrest of the forebrain: "the face predicts the brain" (DeMyer, Zeman, and Palmer, 1964).

**Clefts of the Mandibular Process.** Interference with the normal union of the paired first branchial arches (mandibular arch) as they converge ventrally results in midline mandibular clefts and anomalies of the anterior two-thirds of the tongue. When the mouth is formed, a notch is present in the midline of the lower lip. As the deformity progresses in severity, clefts of the lip and mandibular symphysis, and ankyloglossia can be observed. Cosman and Crikelair (1969) felt that these malformations represent one end of a spectrum of midline branchiogenic syndromes. As the pathologic insult increases, the second, and possibly the third, branchial arch becomes involved. Morton and Jordan (1935) described a 13 day old newborn with a complete form of this midline branchiogenic disorder. The newborn had a cleft of the lower lip and mandible, ankyloglossia, contracture of the neck in the midline, and absence of the hyoid, manubrium, and upper portion of the sternum. Without anterior skeletal support, the trachea and the lungs were free to herniate beneath the skin of the neck and anterior chest. Monroe (1966) concluded after a review of the literature that midline mandibular clefts were best explained by a failure of mesodermal penetration.

**Clefts Associated with the Maxillary Process.** The maxillary process occupies a key position. Budding off the mandibular arch, the maxillary process is brought into contact with the mandibular process, median and lateral nasal processes, and optic placode. Thus, the process has the opportunity to participate in the formation of several facial clefts.

The commissure of the primitive mouth is located at the point of bifurcation of the maxillary and mandibular processes. This lateral slit is gradually obliterated by the progressive fusion of the processes to form the cheek and by the development of the muscles of mastication. By the twelfth week the commissures are formed. Persistence of the furrow between the maxillary and mandibular processes results in a transverse facial cleft, as seen in hemicraniofacial microsomia (see Chapter 54) and Goldenhar's syndrome. A faulty union between the maxillary and globular processes is responsible for the formation of the common clefts of the upper lip.

The central mass of mesoderm of the frontonasal region is separated from the lateral mesodermal masses of the maxillary process by a groove, the naso-optic groove. If the involved masses fail to join properly, the naso-optic groove is transformed into a naso-ocular (nasomaxillary) cleft. The groove contains the future nasolacrimal duct and is confluent with the developing eye. Therefore, associated deformities of these structures are invariably seen. Furthermore, if the maxillary process fails to unite with the globular processes, an oronasooocular cleft would result.

Facial clefts within the maxillary process itself are not as easily explained. These malformations, oro-ocular cleft, and the clefts associated with the Treacher Collins syndrome (mandibulofacial dysostosis) do not coincide with any known embryologic seams. These clefts probably reflect a disturbance in the flow of neural crest cells during their dorsoventral
migration. The resulting paucity of neuroectoderm within the maxillary process produces a weak point which can disintegrate to form a cleft. In the case of mandibulofacial dysostosis, Poswillo (1975) has been able to produce an animal model by the selective destruction of the neural crest stream. A "vacuum" is created in the region of the optic placode. The neural crest cells destined for the optic placode region are considered "late starters". At the time of the derangement, the front-running neural crest cells have presumably already reached the area of the naso-optic furrow. The unsupported area that is subject to a cleft deformity is, therefore, found more proximally in the otomandibular region rather than the naso-ocular junction. Borrowing from this concept, it is conceivable that the destruction of the middle portion of the neural crest cells could produce a mesodermal deficiency in the more ventral section of the maxillary process. A disruption of this weak zone would form the oro-ocular cleft.

Although knowledge of the morphogenesis of rare facial clefts remains incomplete, an even greater gap exists in the understanding of the causal agents responsible for the morphokinetic disturbances.

**Etiology**

To be born normal, the newborn must successfully overcome the possible obstacles associated with unfavorable heredity and hostile intrauterine environmental factors. Aside from the Treacher Collins and Goldenhar syndromes, heredity appears to play a minor role in the formation of most rare craniofacial clefts; the majority of atypical clefts occur sporadically (Fogh-Andersen, 1965).

Accumulating evidence from animal and clinical studies supports the concepts of multiple interacting etiologic factors. The complexity of the problem is underlined by the vast number of teratogenic agents known to produce facial clefts. The study of nonhuman embryos and human statistics has yielded valuable information, but large voids remain in our knowledge of the pathogenesis of rare facial clefts. It should be mentioned that most of the information that is now available is based on studies of the formation of the common clefts of the lip and palate. From these investigations, four major categories of environmental factors have been identified: (1) radiation, (2) infection, (3) maternal metabolic imbalances, and (4) drugs and chemicals (Wilson, 1972).

**Radiation.** Although clefts of the lip and palate can be experimentally produced in animals by the administration of roentgen rays (Warkany and Schraffenberger, 1947; Callas and Walker, 1963; Poswillo, 1968), a similar teratogenic effect in humans has not been verified. An increased incidence of clefts could not be demonstrated in the offspring of Japanese mothers who survived the atomic bombings (Neel, 1958). In a group of 57 women exposed to large doses of atomic radiation in the first 15 weeks of pregnancy, a disproportional rise in the incidence of malformations, other than microcephalic newborns, was not observed (Miller, 1969).

**Infection.** Infectious agents have been implicated in the pathogenesis of congenital malformations in general. In regard to craniofacial malformations, the study of viruses, bacteria, and protozoa has not been particularly rewarding. In animals, the H1 virus has been shown to be capable of producing sporadic occurrences of facial clefts (Ferm and Kilham,
The influenza A virus has also been implicated in an epidemiologic study (Leck and coworkers, 1969). Following an epidemic of this agent, an increased incidence of cleft lip deformities was noted. Although the rubella virus has been demonstrated to produce congenital malformation in man, an increased incidence of facial clefts has not been documented. In studies of the toxoplasmosis protozoan, a two- to four-fold increase in the infestation rate of this agent was found in mothers of offspring with facial clefts (Gabka, 1953; Erdelyi, 1957; Kirovec and associates, 1957). Convincing correlations between bacterial infections and facial clefts have not been reported.

**Maternal Metabolic Imbalance.** Adverse effects on embryonic facial development have been attributed to alterations in maternal metabolism. Tocci and Beber (1970) have presented evidence of an abnormal phenylalanine metabolic pathway in some mothers of offspring with cleft lip and palate. Although it has been stated that diabetic mothers have a greater chance of delivering a newborn with a congenital malformation (Comess, 1969; Pederson, Thigstop, and Pedersen, 1964), a higher frequency of craniofacial clefts has not been described. Manipulation of the thyroxine levels in animals has been shown to influence the frequency of facial clefts. A higher incidence of clefts occurs in the offspring of female rats that have had a partial thyroidectomy (Langman and Van Faassen, 1955). Reversal of this phenomenon has been demonstrated in mice given supplemental thyroxine (Woollam and Millen, 1960). A collaborative study in humans has not been reported.

**Drugs and Chemicals.** An enormous amount of effort has been expended investigating the teratogenic potential of drugs and chemicals. The list of incriminated agents continues to expand (Wilson, 1973). In a parallel fashion, drug consumption by society is ever increasing. Nora and associates (1967) found that a mean of 3.7 potentially teratogenic drugs was taken during the first trimester in a prospective study of a group of 240 pregnancies. The growing list of suspect drugs and the increasing use of these agents might well be responsible for the apparent rise in the number of malformations.

The range of drugs and chemicals known to induce congenital malformations in animals and man is broad. These agents fall into the general categories of anticonvulsants, antimetabolic and alkylating agents, steroids, and tranquilizers.

**Anticonvulsants.** Several statistical studies have shown that mothers who take anticonvulsant medication give birth to a higher number of facially deformed children than a comparable control population (Janz and Fuchs, 1964; Melchior, Svensmark, and Trolle, 1967; German, Kowal, and Ehler, 1970; South, 1972; Spidel and Meadow, 1972). The incidence of facial clefts in infants born to women with seizure disorders is reported as being approximately 1 per cent (Pashayan, Pruzansky, and Pruzansky, 1971; Erickson and Oakley, 1974). The risk is six times greater than that incurred by women without seizure disorders (Erickson and Oakley, 1974). The teratogenic effects of diphenylhydantoin might be related to its antimetabolic effects, since it possesses antifolate properties.

**Antimetabolic and Alkylating Agents.** The teratogenic activity of these drugs is well established. Their clinical relevance, however, is limited, since few embryos survive the lethal effects of these agents. Thiersch (1952) has reported a unilateral cleft lip and palate in a newborn who had been exposed to aminopterin in utero. In animals, vincristine (DeMyer,
1964) and a mild folic acid antagonist, triazene (Murphy, Dagg, and Karnofsky, 1957; Poswillo, 1973), have been shown to produce facial clefts.

**Steroids.** Many investigators have been able to induce clefts of the palate in animals by the administration of steroids (Frazer and Fainstat, 1951; Harris and Ross, 1955; Murphy, Dagg, and Karnofsky, 1957; Walker and Frazer, 1957; Heiberg, Kalter, and Frazer, 1959). Corticosteroids have been shown to reduce the amount of amniotic fluid, which, in turn, could produce detrimental postural changes in the embryo limiting the available intrauterine space (Harris, 1964; Walker, 1965; Frazer, Chew, and Verusio, 1967). Restriction of the normal extension of the head could interfere with the downward displacement of the tongue, an event which is essential to allow the elevation of the palatal shelves. A decreased synthesis of sulfomucopolysaccharides within the palatal shelves is also caused by cortisone, and Larsson (1968) has explained the formation of the clefts on this basis.

**Tranquilizers.** The tragic history of malformations caused by thalidomide is well known. Ear deformities have been documented in the offspring of mothers who ingested thalidomide during pregnancy (Smithells and Leck, 1963; Livingston, 1965). Kleinsasser and Schlothane (1964) reported a study of women who took thalidomide during the first six weeks of pregnancy. During the period of use between 1959 and 1962, at least 1000 severe cases of malformations associated with the first and second branchial arches were observed in the offspring. Approximately 2000 less severely deformed cases were also noted. Poswillo (1973, 1974b) has been successful in reproducing the first and second branchial arch syndrome in primates by means of thalidomide.

Diazepam (Valium), one of the most widely prescribed drugs, has been shown by Miller and Becker (1975) to produce cleft palate in animals. Saxén (1975) and Safra and Oakley have documented a higher incidence of cleft lip, with or without a cleft of the palate, in children of mothers who ingested diazepam during the first trimester. Mothers of infants with oral clefts had used diazepam four times more frequently than mothers of infants with other malformations (Safra and Oakley, 1975).

**Other Agents.** Both thalidomide and triazene, used by Poswillo (1973) to produce an animal model of the first and second branchial arch syndrome, induce a localized hematoma in the otomandibular region. Aspirin and vasopressors are also known to produce hemorrhage in embryos that subsequently develop malformations of the limbs and facial clefts (Warkany and Takags, 1959; Larsson and Broström, 1965; Poswillo and Sopher, 1971; Wilson, 1972; Saxén, 1975). A Treacher Collins-like deformity has also been reproduced in animals by Poswillo (1975) using vitamin A, which can also cause malformations of the brain, eyes, ears, and jaws when administered in variable amounts (Cohlan, 1953; Giroud and Martinet, 1955, 1956, 1957; Poswillo and Roy, 1965; Marin-Padilla, 1966; Morriss, 1972).

The mystery of cyclopian appearance of malformed lambs was solved by a series of investigations performed by Binns and his associates (1959, 1960, 1961). The shepherders called these deformed lambs "monkey-faced". The deformities were found to be caused by a poisonous weed, *Veratrum californicum*, that is found on the grazing lands. Brucker, Hoyt, and Trusler (1963) noted the close resemblance of these face-brain anomalies to the cebocephalic (Gr *kebos*, monkey) and the holoprosencephalic craniofacial deformity seen in humans.
From this review, it can be appreciated that the intrauterine environment might not be as secure and comforting a milieu for the embryo as one would like to believe. The major part of the face is developed during a period in which the mother could be unknowingly pregnant. Thus, even if the teratogenic potential of all drugs were known, malformations might still not be prevented. The embryo might be able to elude the teratogenic effects of a single agent only to have the balance tipped against it by a combination of drugs. Those embryos subject to a genetic factor face an additional handicap.

**Morphopathogenesis**

Several pathways exist through which the various causal agents can exert their detrimental forces. Interference with cell formation, cell replication, or cell migration by the etiologic forces could produce rare craniofacial clefts.

Those who favor the fusion theory explain the morphogenesis of a facial cleft on the basis of the failure of the various processes to achieve contact. Any retardation or restriction of the movements of the processes could result in spatial malalignment and, thereby, could physically prevent normal union. Drugs which disturb the metabolic rate and affect the properties of the ground substance could intrinsically alter the normal development and movement of the various processes. Spatial restrictions, such as those imposed by oligohydramnios, could apply an extrinsic restraint on the facial processes and thus mechanically interfere with their normal fusion.

Alterations in the normal equilibrium between cell formation and spontaneous cell death is another possible means of cleft formation. Warbrick (1963) suggested that unwanted cells are normally discarded during the fusion process. Conceivably, two processes could meet and not coalesce if the programmed death of the epithelial cells does not occur to allow the mesenchyme to stream across. A partial interruption of this turnover cycle could lead to the formation of an incomplete cleft.

The concept of an altered metabolic rate and premature cell death is equally applicable to the mesodermal penetration theory. If the ability of the cell to replicate and migrate is thwarted, weak areas susceptible to cleft formation can be created.

Arrest or turbulence in the dorsoventral flow of neural crest cells is an attractive theory proposed by proponents of the mesodermal penetration school. Incomplete filling of the "epithelial wall" caused by these pathologic disturbances would produce an unsupported fragile zone. Hövels (1953) felt that the early central disorganization of the neural plate or the neural crest is responsible for the Treacher Collins syndrome. Subsequently, Johnston (1964) experimentally produced a facial cleft by removing a portion of the neural crest before the cells began their migration. This concept gained additional support with the work of Poswillo (1975). His animal experiments suggested that bilaterally symmetrical facial clefts, such as in the Treacher Collins syndrome, are best explained by the disorganization of the preotic neural crest cells approximately at the time of their migration into the first branchial arches. The proliferation rate of the neural crest cells has also been implicated. A reduced rate in neural crest cell proliferation is present in the frontonasal mesenchyme of the mouse embryo with the Dancer gene, and a Waardenburg-like syndrome is produced in these animals (Trasler, 1969). In humans, the white forelock of hair seen in patients with Waardenburg...
syndrome can be explained by the patchy degeneration of the neural crest cells, since these cells also give rise to the melanocytes (Johnston, 1975).

Disturbances in the circulatory system could also reduced the volume of tissue and limit the ability of mesenchymal penetration. Tandler (1902) and Kundrat (1882) are cited by Sanvenero-Rosselli (1953) as being among the first to associate an arterial malformation with a congenital anomaly. An arhinencephalic malformation was described by Kundrat (1882), which he causally linked to a vascular disturbance in areas supplied by the anterior cerebral artery. Streeter (1922) used the term "focal fetal deficiencies" to explain congenital malformations. He felt these deficiencies were due to chromosomal aberrations. Keith (1940a), however, felt that it was more profitable to explain "Streeter's foetal dysplasia" as a local vascular disturbance. He postulated that the failure of circulatory anastomosis between and within the various facial processes was the responsible underlying pathologic mechanism. Because of the inadequate vascular supply, a "dysplastic crease" or "necrotic groove" was created and led to the formation of a partial or complete facial cleft. Frazer (1940) also mentioned the possible detrimental effect of local ischemia during the early phases of embryonic development.

In terms of the ischemic crisis theory, the first and second branchial arch syndrome is the best studied malformation. In 1929, Lockhard described an anomaly of the maxillary artery and associated it with deformities of the zygoma, middle ear, and muscles of mastication. In 1940, Braithwaite and Watson suggested that the ischemic crisis was caused by a maldevelopment or total absence of the stapedial artery. McKenzie and Craig (1955) elaborated on this theory and pointed out the vulnerability of the stapedial artery. The artery, which is short-lived, supplies the first and second branchial arches. After branching off the dorsal aorta of the primitive circulatory, the artery makes its appearance on the 33rd day, and seven days later it disappears. The blood supply to the area is then furnished by the external carotid artery as a transfer of the main arterial trunk occurs from the dorsal aorta to the ventral aorta. An interruption in this orderly transition could lead to a circulatory crisis. The theory of McKenzie and Craig is based on a postmortem dissection of a 10 week old newborn with Treacher Collins syndrome. The maxillary artery was observed to have "petered out" before it reached the pterygomaxillary fissure. Normal mandibular, posterior superior alveolar, and middle meningeal branches had been given off. McKenzie (1958) later used this theory of stapedial artery formation to explain the deformities of the first and second branchial arch syndrome, Pierre Robin anomalad, cleft lip and palate, hypertelorism, and congenital deaf mutism. Not all investigators would agree with this expanded application of the stapedial artery theory.

Poswillo (1973) suggested that a localized embryonic hemorrhage rather than anomalous development of the stapedial artery best explains the structural deformations found in the first and second branchial arch syndrome. In animal experiments, the hemorrhage occurs in the vicinity of the first and second branchial arches shortly after the formation of the stapedial artery. Depending upon the magnitude of local tissue destruction and the extent of delay in differentiation, varying degrees of maldevelopment can be observed.

The role of heredity in the causation of rare craniofacial clefts remains to be clarified. The influence of heredity is most clearly defined in the Treacher Collins syndrome (see Chapter 550. Rogers (1964a) offered some interesting ideas to explain the incomplete and
complete forms of this syndrome. The responsible gene is known to have a variable penetration ability. Taking this into consideration, Rogers suggested that a "strong" gene exerts its influence early in the course of facial development. Thus, a more comprehensive expression of the aberrant gene occurs, and the "complete" form of the syndrome is seen. A "weak" gene exerts its inhibitory action at a later stage of embryonic development. Hence, an "incomplete" milder form of the syndrome is seen. The area of disturbance is thought to be another factor that influences the clinical expression of the anomaly. In the milder forms of the syndrome, the deleterious effects of the offending gene are felt to be confined, more or less, to the maxillary portion of the first branchial arch. Conversely, the complete form of the syndrome entails involvement of both the maxillary and mandibular portions of the first arch, as well as some of the structures derived from the second branchial arch.

In the final analysis, it can be safely stated that the causal environmental and heredity factors have potential access to multiple pathways in which to exercise their influences. The teratologist, confronted with the problem of multiple factors acting through numerous channels, assumes an enormous burden when he is asked to explain the formation of a particular cleft. The problem, moreover, is compounded by the lack of a universally accepted classification system.

**Classification**

The task of classifying rare craniofacial clefts is not a simple one. Several major handicaps must be overcome. Because the clefts are so rare, reviews of the literature are often used to gather descriptive material of the malformations. Unfortunately, descriptions of the individual cases are often incomplete. Furthermore, the diverse groups of specialists involved in the study of these malformations frequently use different terminology for the same deformity. In addition, the observer can be confused by the wide variety of facial clefts that can exist in numerous combinations to distort the face into bizarre forms. Fortunately, the majority of the atypical craniofacial clefts are easily recognizable as belonging to a particular group. Although the challenge is admittedly difficult, several attempts have been made to bring order out of chaos.

**American Association of Cleft Palate Rehabilitation Classification.** In 1962, Harkins and his associates proposed a classification system endorsed by the American Association of Cleft Palate Rehabilitation (AACPR). The rare facial clefts are divided into four major groups: (1) mandibular process clefts, (2) naso-ocular clefts, (3) oro-ocular clefts, and (4) oroaural clefts.

Clefts of the lower lip, mandible, and lip pits are included in the mandibular process clefts group. The naso-ocular clefts extend from the alar region toward the medial canthus. Clefts of the oro-ocular group connect the oral aperture to the palpebral fissures. This group is subdivided into oromedial canthus and orolateral canthus clefts. The temporal extension from the lateral canthus is included in the orolateral canthus subdivision. The oroaural clefts are directed from the corner of the mouth toward the ear to form the last main group.

The AACPR classification system suffers in several respects. Conspicuously omitted are the major midfacial clefts and the Treacher Collins deformity. Confusion in terminology is also noted. The oromedial canthus cleft is described in the original text but is illustrated
as an oronasal-ocular cleft. Furthermore, the classification is based on the surface anatomy of the deformity and fails to describe the underlying skeletal components of the clefts.

Boo-Chai (1970) recognized the deficiencies of the AACPR description of the oro-ocular cleft. Morian (1887) was the first to recognize the anatomical differences between the clefts by drawing attention to the importance of the infraorbital foramen. Using this landmark, Boo-Chai subdivided the oro-ocular clefts into types I and II. In contrast to the naso-ocular cleft, the oro-ocular clefts do not violate the pyriform aperture. The soft tissue components of the clefts further distinguish the two types.

In the type I cleft, the cleft of the upper lip is seen to begin lateral to the Cupid's bow. Hence, the departure point is found lateral to that of the common cleft lip. The defect courses lateral to the nasal ala onto the cheek to end in the medial canthal region. According to Boo-Chai, an extension of the cleft from the lateral canthus can occur into the temporal region. On the facial skeleton, the type I cleft begins between the lateral incisor and cuspid and does not encroach upon the pyriform aperture. It continues medial to the infraorbital foramen to enter the inferomedial aspect of the orbit.

On the other hand, the type II oro-ocular cleft starts near the corner of the mouth and terminates as a coloboma in the midportion of the lower eyelid or near the lateral canthus. The bony cleft is found in the region of the bicuspid and takes a path lateral to the infraorbital foramen to enter the inferolateral portion of the orbit.

Karfik Classification. Karfik (1966) proposed a detailed classification of rare craniofacial clefts based on embryologic and morphologic criteria. A revised form of portions of this classification was presented the following year. Five major groups (A to E) are outlined (Table 46-1).

Clefts of Group A are composed of malformations of the "rhinocephalic region". The group is subdivided into Group A 1 (axial) and Group A 2 (para-axial) malformations. The "axial" subgroup includes the deformities of the frontonasal prominence structures. The "para-axial" subgroup encompasses the anomalies of the adjacent regions, which are "always combined disorders in the development of the nose and its parts". The oro-ocular clefts are included in this group, since Karfik feels that they begin from "typical lip clefts". However, Boo-Chai (1970) noted that the cleft of the lip associated with this deformity is actually located lateral to the location of the common cleft lip.

Comprising the group B malformations are those deformities related to the first and second branchial arches. The subdivision of this group, Group B 1, is composed of the "lateral otocephalic" disorders, which include hemicraniofacial microsomia, Pierre Robin anomaly, Treacher Collins syndrome, and auricular malformations. The midline mandibular malformation falls in the group B 2 subdivision.

The Group C disorders include malformations of the orbitopalpebral region. Located in the Group D disorders are the "craniocephalic" malformations such as Apert's and Crouzon's diseases. The final category, Group E, consists mainly of atypical deformities caused by congenital tumors, atrophy, and hypertrophy which are more closely associated with facial asymmetry problems than with cleft formations. The oblique facial cleft is also included
in this group and is termed by Karfik a "true oblique cleft" since it cannot be related to any known embryonic facial seam. This cleft is similar to the type II oro-ocular cleft (Boo-Chai).

**Table 46-1. Karfik Facial Cleft Classification**

**Group A - Rhinencephalic Disorders**

| Axial (A 1) | Prolapse       | Meningocele |
|            |                | Glioma      |
|            |                | Dermoid cyst|
|            |                | Teratoma    |
| Clefts     | Medial nasal (double nose) | |
|            | Median cleft of upper lip and premaxilla | |
| Defects    | Coloboma of nostril | |
|            | Partial of nose   | |
|            | Total of nose     | |
|            | Septal            | |
|            | Atresia nasi      | |
| Para-axial (A 2) | Clefts | Coloboma, iridic or palpebral |
|            | Total or partial para-axial | |
|            | Cleft lip, typical | |
|            | Lacrimal duct dystopia | |

**Group B - Branchiogenic Disorders**

| Lateral otocephalic (B 1) | Clefts | Macrostomia |
|                          |       | Lateral cervical fistula |
|                          | Dysostosis | Mandibular (eg, Pierre Robin) |
|                          |           | Mandibulofacial (eg, Treacher Collins) |
| Defects                  | Partial or total auricular | |
|                          | Atresia | |
| Medial axial (B 2)       | Clefts | Lower lip |
|                          |         | Mandible |
|                          |         | Fissura colli medialis |
|                          |         | Fissura thoracis medialis |

**Group C - Ophthalmo-Orbital Disorders**

| Malformation | Eyeball: | microphthalmia |
|             |         | anophthalmia |
|             | Lids:   | blepharophimosis |
|             |         | epicanthus |
|             |         | ptosis |
|             |         | agenesis |
| Defect      | Orbital | |
| Clefts      | Upper lid coloboma | |
|            | Commissural | |
**Group D - Cranioccephalic Disorders**

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Head and face (eg, Apert's and Crouzon's diseases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect</td>
<td>Scalp</td>
</tr>
<tr>
<td></td>
<td>Skull</td>
</tr>
</tbody>
</table>

**Group E - Atypical Facial Disorders**

- Oblique facial clefts
- Dysembryoma, parasite
- Hemifacial atrophy
- Hyperplasia
- Neoplasm, congenital
- Teratoma

Classification of Median Facial Clefts. Two broad categories of median facial anomalies exist: (1) those in which there is a deficiency of tissue, thereby creating an absence of parts, and (2) those in which the amount of tissue is near normal or in excess, but associated with a malformation.

Tissue Deficiency Malformations. The median facial anomalies with a shortage of tissue have been called arhinencephaly malformations. This term was used by Kundrat (1882) to express the absence of the olfactory bulbs and tract which were assumed to be the common malformation in this series of brain abnormalities. Investigators subsequently have established that the underlying developmental error is the arrested cleavage of the forebrain (prosencephalon) (Yakovlev, 1959; DeMyer, Zeman, and Palmer, 1964). DeMyer and his associates (1964) proposed the term holoprosencephalon to denote the fact that the prosencephalon tends to remain "holistic" when cleavage does not normally occur. As mentioned before, an intimate relationship exists between the median facial structures and the forebrain. Therefore, the severity of the facial disorganization reflects an equally severe brain anomaly. Based on this face-brain theme, the holoprosencephalic malformations are divided into five types (Table 46-2). The table has been modified to incorporate some of the concepts of Cohen and his associates (1971a). To emphasize further this brain-face relationship, Brucker, Hoyt, and Trusler (1963) proposed the term median cerebrofacial dysgenesis.

Near Normal and Excess Tissue Disorders. In direct contrast to the tissue deficiency disorders, this group of median facial anomalies does not have a high predictive correlation between the distorted face and the underlying brain. The amount of tissue in the midline is near normal or in excess. The spectrum of deformities ranges from a slight midline notch of the upper lip to the severest form of orbital hypertelorism. Between these two extremes, a diverse group of deformities is found.

Median cleft face syndrome is the term favored by DeMyer (1967) for this group of malformations (see Chapter 56). The seven features of the entity are: (1) orbital hypertelorism, (2) V-shaped frontal hairline, (3) cranium bifidum occultum, (4) median cleft of the upper lip, (5) median cleft of the premaxilla, (6) median cleft of the palate, and (7) primary telecanthus. DeMyer concluded that the probability of mental retardation is low when orbital hypertelorism is combined with one or more of the six remaining features. The chance of mental normalcy
diminishes when the orbital hypertelorism is excessive and is the sole facial anomaly or when it is combined with an extracephalic anomaly.

**Table 46-2. Types of Holoprosencephaly**

<table>
<thead>
<tr>
<th>Facial Type</th>
<th>Facial Features</th>
<th>Cranium</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Cyclopia</td>
<td>Single or partially divided eye in single orbit or anophthalmia; arhinia or double proboscis</td>
<td>Microcephaly</td>
<td>Alobar</td>
</tr>
<tr>
<td>II. Ethmocephaly</td>
<td>Extreme orbital Hypotelorism with separate orbits; arhinia or a single or double proboscis</td>
<td>Microcephaly</td>
<td>Alobar</td>
</tr>
<tr>
<td>III. Cebcephaly</td>
<td>Orbital hypotelorism; proboscis-like nose</td>
<td>Microcephaly</td>
<td>Usually alobar</td>
</tr>
<tr>
<td>IV. With median cleft lip (premaxillary agenesis)</td>
<td>Orbital hypotelorism; flat nose; absent median portion of upper lip</td>
<td>Microcephaly; sometimes trigonocephaly</td>
<td>Usually alobar</td>
</tr>
<tr>
<td>V. With median philtrum-preamxilla anlage</td>
<td>Orbital hypotelorism; bilateral cleft lip; flat nose</td>
<td>Microcephaly; sometimes trigonocephaly</td>
<td>Semilobar or lobar</td>
</tr>
</tbody>
</table>

For the same group of anomalies, Sedano and his associates (1970) preferred the term frontonasal dysplasia. They considered frontonasal dysplasia and Holoprosencephaly malformation to be at opposite ends of the medial facial anomaly spectrum. Differences in embryopathogenesis and clinical features form the basis of their reasoning. Although the bifid nose is generally accepted as part of this clinical complex, unilateral and bilateral nasal clefts are included in the frontonasal dysplasia classification system. This is a debatable addition, since the nasal alar clefts are not true midline deformities.

Although orbital hypertelorism is frequently associated with the median cleft face syndrome (frontonasal dysplasia), other nonmidline malformations can cause an increase in interorbital distance. For a discussion of orbital hypertelorism see Chapter 56.

**Tessier Classification.** Tessier presented a classification of craniofacial clefts before the Second International Congress on Cleft Palate in Copenhagen in 1973. The new classification system has several unique features of merit. It is based on the personal experience and observation of the investigator rather than on a collection of examples culled from a review of the literature or hospital records. Therefore, the terminology and quality of observations remain uniform. In addition, the classification system successfully integrates the findings of the clinical examination with the underlying skeletal deformity observed directly at the time of reconstructive plastic surgery. From the treatment standpoint, the correlation
of the clinical appearance with the surgical anatomy increases the value of the classification for the practicing plastic surgeon.

**Cleft Numbering System.** The clefts are numbered from 0 to 14 and follow constant lines or axes through the eyebrows or eyelid, maxilla, nose, and lip.

The orbit is regarded as the reference landmark, since it is common to both the cranium and the face. Clefts that are located cephalad to the palpebral fissure are directed "northbound" and considered to be mainly "cranial" in nature. The "southbound" clefts pass caudally from the palpebral fissure to become "facial". "Craniofacial" clefts are formed by the combination of northbound and southbound clefts. The craniofacial clefts usually follow the same well-defined "time zones". Thus, the following combinations can be clinically observed: 1-14, 1-13, 2-12, 3-11, and 4-10. Although the craniofacial clefts tend to coincide with these "time zones" across the orbit, the vascular supply and embryonic processes do not necessarily follow the same north-south pathways. Consequently, the embryopathogenesis of some of the rare craniofacial clefts is difficult to explain.

It is important to keep the "time zone" concept in mind during the examination of the patient. The "time zone" principles disciplines the clinician to search for malformations along the entire axis. Unsuspected and often overlooked soft and bony tissue anomalies will be discovered when an examination is conducted in this manner. For example, note that the common cleft lip is part of cleft No 1, 2, and 3. When this relatively common cleft lip deformity is encountered, the clinician should be alerted to examine the more cephalic structures with care. The combination of a bilateral cleft lip with a porcine-type nose illustrates the point. The porcine nostril is usually associated with a short frontal process of the maxilla, which is a feature of the No 3 cleft. A slight medial canthal dystopia and excessive tearing, indicative of an obstructed lacrimal apparatus, might be detected on closer examination. A forme fruste of an oronasal-ocular cleft would thus be discovered. Whitaker, Katowitz, and Randall (1974) have shown that malformations of the nasolacrimal system are associated with the common facial clefts at a much higher frequency than is generally accepted.

**The Degree of Cleft.** The clinical expression of the craniofacial cleft is highly variable. The face can be marred by a faint line of a microform or can be disfigured by a full representation of the gaping cleft. The extent of involvement of the soft tissue and skeletal component is also variable, and they are seldom affected with equal severity. Furthermore although closely related, the soft tissue component of the cleft does not always coincide with the skeletal fault. Therefore, descriptions of the clefts that are based on the bony malformation are more reliable, since the skeletal landmarks tend to be more constant.

Facial clefts located lateral to the infraorbital foramen, as a general rule, have proportionally greater bony disruption than the clefts found between the foramen and the midline. Of course, digression from this general pattern exist, the No 3 cleft being a good example.

Unilateral or bilateral forms of the clefts are found. When they are bilateral, atypical craniofacial clefts from different groups can be found on either side.
Description of Clefts

Clinical Varieties of Clefts

The external clinical features of each of the clefts are readily apparent. It is important to consider the variations that can exist in both the extent of the cleft and the involvement of the embryologically related structures. These factors influence the plan of treatment and, therefore, should be recognized during the evaluation of the individual case. The strength of the Tessier classification is that it takes into consideration these variables, emphasizes the underlying skeletal deformity, relates the cleft to the neighboring deformities, and is treatment-oriented. Because of the practical nature of this classification, the rare craniofacial clefts will be described using this system.

No 0 Cleft. The No 0 cleft falls in the midline of the cranium and face. It includes most of the midline deformities described in the other classification systems: Group A 1 axial cleft (Karfik), median cleft face syndrome (DeMyer), frontonasal dysplasia (Sedano), and holoprosencephaly (DeMyer).

The upper lip deformity is represented by a true or false median cleft lip. In the true median cleft lip deformity, similar to the "harelip" seen in rodents, the split occurs between the median globular processes, as opposed to an agenesis of the globular processes as found in a false median cleft.

The true median cleft lip was first described by Bechard in 1823 according to Galanti (1961). Keith (1909) reported a similar deformity found in a specimen located in the Museum of the Royal College of Surgeons in London. Over 100 examples have subsequently been reported, including those by Davis (1935), Weaver and Bellinger (1946), Braithwaite and Watson (1949), Kazanjian and Holmes (1959), Burian (1960), Fogh-Andersen, (1965), Baibak and Bromberg (1966), DeMyer (1967), Scrimshaw (1967), Millard and Williams (1968), and Warkany, Bofinger, and Benton (1973).

Minor degrees of notching of the vermilion border of the lip can be connected to a vertical congenital band extending to the columella, drawing the midportion of the lip cephalad. The cleft often involves the entire vertical dimension of the lip. The labial frenulum is frequently duplicated, and a wide diastema between the central incisors is almost invariably present. The cleft can continue posteriorly in the midline of the premaxilla and less frequently through the secondary palate. When the cleft involves the skeletal framework, a duplication of the anterior nasal spine and angulation of the teeth toward the midline are seen.

The nose is often bifid. Grooving and increased width of the columella are common. The nostrils are intact but can be asymmetrically deformed. The alar and upper lateral nasal cartilages are displaced laterally and are distorted or hypoplastic. The bifid nose is associated with a wide median furrow. In severe cases, Krikun (1972) described a thick subcutaneous fibromuscular band between the hypoplastic alar cartilages and the frontal bone. The band pulls the columella upward. Early excision of the strip is suggested to allow a more normal development of the nasal tip region.
The skeleton of the nasal bridge is broad and flattened. Studies of the osseous structures by Brejcha and Fára (1971) and Krikun (1972) showed the nasal bones to be large and thick. The nasal septum is thickened, duplicated, or even absent. The frontal processes of the maxilla tend to be well developed. The ethmoid cells are increased in number and enlarged (Converse and associates, 1970). The posterior ethmoid cells and the sphenoid sinus are usually not enlarged. The cribriform plate is low and is only exceptionally enlarged. The distance between the optic canals is usually within the normal range. Orbital hypertelorism is seen as the cleft encroaches into the interorbital space. The cleft continues into the cranium as the No 14 cleft.

If agenesis or hypoplasia is the predominant theme, a false median cleft of the lip is seen. A partial or total absence of the philtrum and premaxilla can occur. The term "false median cleft" was proposed for this deformity by Braithwaite and Watson (1949). The description of the first reported case is credited by Fogh-Andersen (1965) to Bartholin, who described the deformity 300 years ago. In a review by DeMyer, Zeman, and Palmer (1964), 75 cases were collected from the literature.

The wide central deficiency of the entire height of the upper lip extends into the floor of the nose. The nose falls to develop properly, and the columella is absent or rudimentary. The nasal septum is vestigial and unattached to the palate at any point. A cleft of the secondary palate is often present. The nose is depressed and indented at the tip. At the other extreme, the nose may be totally absent or represented by a proboscis. The nasal bone and the septal cartilages were noted to be absent in the six patients reported by Brucker, Hoyt, and Trusler (1963). The median bony deficit extends into the ethmoids to produce orbital hypotelorism or cyclopia. The cleft is often associated with eye deformities, congenital absence of the skin of the vertex of the scalp, and congenital forebrain deformities, especially in the region of the olfactory bulbs. The associated brain malformation generally limits the life to infancy. Most of the patients die within the first three months and rarely live to be a year. As the severity of the deformity decreases, the chance of normalcy improves (Yakovlev, 1956). Those patients with the mildest improvement have the potential to be intellectually near normal (DeMyer and Zeman, 1963; Converse, McCarthy, and Wood-Smith, 1975).

Median clefts of the lower lip and mandible coincide with the caudal extension of the No 0 cleft. Although these clefts fall on the No 0 cleft meridian, Tessier has tentatively labeled them No 30 clefts. This group would include the mandibular process clefts (AACPR classification), branchiogenic medial axial B 2 clefts (Karfik), and the midline branchiogenic syndrome (Cosman and Crikelair).

Couronné (1819) first described the median cleft of the lower jaw. Subsequently approximately 50 cases have been reported (Monroe, 1966; Cosman and Crikelair, 1969; Fujino, Yasuko and Takeshi, 1970).

The cleft of the lower lip can be limited to the soft tissue. In its most minor form, a notch in the lower lip is present. More frequently, however, the cleft extends into the bony mandibular symphysis. As the severity of the malformation increases, the neck structures, hyoid bone, and even the sternum are progressively involved. The anterior portion of the tongue is often bifid and bound to the divided mandible by a dense band of fibrous tissue. The medial margins of the bifid tongue are attached along the length of the cleft of the
alveolar ridge (Stewart, 1935). Millard and associates (1971) reported 32 cases associated with ankyloglossia and 10 cases with clefts of the tongue. Total absence of the tongue has also been associated with the mandibular midline clefts (Rosenthal, 1932; Herren, 1964). The cleft of the alveolus is located in the midline and passes between the central incisors.

Although the major deformity is due to the failure of a midline union of the first branchial arch, associated deformities of the neck caused by failure of fusion of the lower branchial arches are not uncommon. The hyoid bone is often absent. Failure of proper development of the thyroid cartilage can also occur. The anterior strap muscles of the neck are atrophic and replaced by a dense contracted fibrous cord holding the chin in flexion. In addition, bulging at the neck and sternal regions during straining is seen when the structures of the anterior neck are thin and hypoplastic and fail to support the trachea and lungs. In these severe forms, the clavicles are widely spaced, and the manubrium sterni is absent.

By tentatively labeling the mandibular midline deformities as No 30 clefts, Tessier keeps the classification open. This feature allows the addition of related deformities of the branchial arches. For example, a patient described by Abramson (1952) had a bilateral paramedian cleft of the mandible. A tooth bud was found in the intervening segment of tissue. This is an extremely rare malformation which, probably in the strictest sense, should not be considered a midline cleft. In 1973, Gardner, Kapun, and Jordan reported a similar deformity that was confined to one side of the midline. Equally rare deformities such as duplication of the mandible could be added to this group of clefts.

The mandibular cleft can be associated with deformities of other facial structures. Six mandibular clefts with related deformities of the upper face have been reported. Weyer (1963) and Monroe (1966) described two patients who had clefts of the soft palate. A stillborn infant reported by Ashley and Richardson (1943) had a cleft of the upper lip and palate. The case published by Gardner and associates had a bilateral cleft of the maxillary alveolus. The remaining patients had a median cleft of the upper lip (Schalbe, 19130, hemicraniofacial microsomia (Braithwaite and Watson, 1949), or a dermoid of the nose (Wolfler, 1890).

Duplication of the midline facial structures is indeed rare. Potter (1975) listed this malformation under the broad category of conjoint twins as a monocephalic partial duplication and illustrated a case. Goulian and Conway (1964) reported a similar attempt of facial duplication in a female infant. The infant also had hydrocephalus and died during the eighth week of life. An autopsy showed hydrocephalus of an advanced degree and severe cerebral atrophy. Duplication of the cranial vault, brain, or extrafacial structures was not seen. The most detailed description of this malformation is that of Calaycay, Gooding, Brown, and Herhahn (1976). Their female patient was a product of a full-term pregnancy and had no deformities other than those of the craniofacial region. A bulky, protruding, fleshy, soft tissue mass occupied the macrostomia. The right side of the cranium and face was larger than the left. The anterior fontanelle was enlarged. Pneumoencephalography showed an elevation and increased width of the third ventricle along with a wide displacement of the lateral ventricles that were diagnostic of agenesis of the corpus callosum (Stiehm, 1972). The fourth ventricle extended from the foramen magnum to the level of the third cervical vertebra, suggesting the presence of Chiari II malformation of the hindbrain. The eyes were in a hyperteloric position with an intervening broad, flat nose. The columella was 3 cm wide. What appeared to be
eyelashes were found along the inferior border of a midline infranasal sinus. The sinus terminated in a blind pouch and was lined with respiratory epithelium.

Bilateral bony struts that traversed the oral soft tissue mass held the jaws apart. The oral mass was shown histologically to contain skin and subcutaneous fat. The duplicated mandible had a W-shape, as did the maxillary arch. The central limbs of the maxillary alveolar arch each contained three teeth that resembled incisors and cuspids. In the region of the soft palate, an irregular bony mass was found which was felt to represent a rudimentary hard palate or vomer. The soft palate terminated with four uvulae of variable size. The anterior half of the tongue was bifid, and the right side was elevated by an enlarged sublingual gland.

**No 1 Cleft.** Before Tessier's observation, the No 1 cleft had not been recognized as a distinct entity. It had been "lumped together" with median clefts and has successfully eluded individual identification in the Group A 1 axial cleft (Karfik), median cleft face syndrome (DeMyer, and frontonasal dysplasia (Sedano) classification syndromes.

The No 1 cleft begins in the Cupid's bow region, similar to a common cleft of the upper lip, and passes through the dome region of the nostril. It extends onto the nose and continues "northbound" along the medial edge of the eyebrow into the cranium as a No 13 cleft. The notch in the dome of the nostril is a distinct feature (Tessier, 1973). The medial canthi per se are not directly involved, but the surrounding distortion can produce a medial canthal dystopia. An associated hypertelorism is often seen.

The skeletal component of this cleft is also unique. The cleft passes between the central and lateral incisors and extends into the nasal cavity by traversing the pyriform aperture just lateral to the anterior nasal spine. The septum is spared. The cleft is directed through the nasal bone, which in severe cases is absent. An alternate route of the cleft is through the junction of the nasal bone and the frontal process of the maxilla. The cleft does not cross through the frontal process of the maxilla per se, but the process is secondarily displaced and flattened. Contributing to the development of orbital hypertelorism is the involvement of the ethmoidal labyrinth.

**No 2 Cleft.** This cleft is notably rare. Only three cases have been seen by Tessier (1975). A question exists as to whether this cleft is a distinct deformity or a transitional form between clefts No 1 and 3. The cleft was therefore represented as a dotted line in Tessier's original drawings. Nevertheless, the cleft does have unique soft and hard tissue characteristics. Like the No 1 cleft, the No 2 cleft had not been previously described as a separate entity.

When present, the associated cleft of the lip lies in the area of the common cleft of the lip. The location of the deformity on the nostril rim is a distinguishing feature of the cleft. The midline third of the nostril is hypoplastic, in contrast to the dome area of the No 1 cleft and the alar region of the No 3 cleft. The nostril deformity is not a true notch. On the affected side, the lateral part of the nose is flattened. The palpebral fissure is not involved as it is in the No 3 cleft. Orbital hypertelorism, however, is seen, and the nasal bridge is broad. Distortion of the eyebrow occurs just within its medial border as the cleft continues into the frontal region as the No 12 cleft. The location of the eyebrow coloboma also serves to distinguish the cleft from its neighbors.
On the facial skeleton, the cleft traverses the alveolus in the region of the lateral incisor to encroach upon the pyriform aperture. The nasal septum is again spared but is deviated by the surrounding distortion. Normal septation between the nasal cavity and the maxillary sinus is present. A notch is seen near the junction of the nasal bone with the frontal process of the maxilla. The frontal process of the maxilla is generally broad and flat but not traversed by the cleft. In contrast to the No 3 cleft, the nasolacrimal system is not disrupted. Enlargement of the ethmoidal labyrinth is responsible for the orbital hypertelorism.

Heminasal atrophy, proboscis lateralis, and supernumerary nostrils fall within the territory of the No 1 and 2 clefts. The No 3 cleft becomes involved when the anomaly extends into the lacrimal apparatus.

**No 3 Cleft.** Unlike clefts No 1 and 2, the No 3 cleft is a well-known entity. Beginning with this cleft, the orbit becomes involved.

Confusion is created by the various names that have been applied to this malformation. Many authors have given their own interpretation of the deformity and have used the same terminology for similar but distinctly different malformations. The nomenclature committee of the AACPR defined the cleft as a naso-ocular cleft which is "a fissure extending from the nasal region toward the medial angle of the palpebral fissure". This cleft has also been categorized as a Group A 2 para-axial cleft (Karfik), a nasomaxillary cleft (Gunter, 1963), an oblique facial cleft (Sakurai, Mitchell, and Holmes, 1966), and more commonly as an oronaso-ocular cleft. Tessier (1969a, b) also used the term oblique facial clefts before proposing his present classification system. The label oblique cleft is particularly ambiguous, since it has been applied to several clefts. The designation No 3 cleft would eliminate this discord in nomenclature.

The first case reported in the literature was by Morian (1887). Subsequently, additional cases have been reported by Davis (1935), Gunter (1963), Ergin (1966), Sakurai, Mitchell and Holmes (1966), Tessier (1969a), Boo-Chai (1970), and Dey (1973).

The cleft lies in the region of the union of the median nasal, lateral nasal, and maxillary processes. Various explanations of the deformity include the lack of fusion of the various processes, insufficient mesodermal penetration, and failure of the naso-optic groove to invaginate and form the tubular nasolacrimal system (Mann, 1964). The unilateral, bilateral, complete, and incomplete forms can coexist.

The cleft of the lip is located in the same region as the common cleft of the lip. This, this characteristic is shared by clefts No 1, 2, and 3. In the nasal area, however, the No 3 cleft changes its course and undermines the base of the nasal ala. A coloboma of the nasal ala represents a mild expression of the malformation. The vertical distance between the alar base and the medial canthus is decreased. The underlying nasolacrimal system is disrupted, leading to a nasolacrimal duct that is blocked and a sac that is prone to repeated infections (Gunter, 1963). The lower canaliculus is malformed and beyond repair (Tessier, 1969a).

The malformations of the ocular region are usually characteristic. The medial canthus is displaced inferiorly. The colobomas of the lower eyelid are found medial to the punctum. The medial canthal tendon is hypoplastic, and its insertion is inferiorly displaced. Involvement
of the eye itself is variable. The problem of restoring facial symmetry is compounded when microphthalmos is present. Damage to a fairly normal eye can occur when it is left unprotected by the associated eyelid deformity. The "northbound" prolongation of the cleft into the medial third of the upper eyelid and eyebrows and onto the forehead is represented by the No 11 cleft.

The osseous component of the cleft passes through the alveolus between the lateral incisor and the cuspid. The lateral border of the pyriform aperture is involved, and an absence of septation between the nasal cavity and maxillary sinus can occur. In contrast to the No 2 cleft, the frontal process of the maxilla is disrupted as the cleft terminates in the lacrimal groove. Complete absence of the frontal process of the maxilla is often seen. Thus, in the severest form of the cleft, the orbit, the nose, the maxillary sinus, and the mouth are confluent. The facial features are considerably distorted and the skeletal disruption is extensive when the cleft is bilateral.

Boo-Chai (1970), in his extensive review article, found 12 cases reported in the world literature. Tessier (1969a) described the findings and treatment of 16 patients with "oblique" (No 3 cleft) and "vertical" (clefts No 4 and 5) clefts, but did not specify the details of each case. Four more cases were added by Dey (1973). The occurrence of the No 3 cleft is certainly greater than that reported in the literature. This is especially true if the incomplete form, such as a coloboma of the nasal alar base, were also included. It is important for the clinician to recognize the full meaning of the mild forms. Search should be made for malformations of the nasolacrimal system and deformities of the underlying skeleton.

From analysis of the cases that are described in sufficient detail, the following can be concluded. Nearly equal distribution of the cleft between the sexes is observed. The side of involvement is also approximately equal, a third occurring on the right, a third on the left, and a third bilaterally. When it is bilateral, a No 4 and 5 cleft is often seen on the contralateral side.

**No 4 Cleft.** Starting with the No 4 cleft, a departure of the deformity from the median facial structures is noted. The cleft moves on to the cheek and is sometimes called meloschisis.

The cleft has been classified as an oro-ocular (AACPR) or oro-ocular type I (Boo-Chai, 1970), a Group A 2 para-axial (Karfik), and a vertical facial cleft by Tessier in his earlier publications (1969a, b). The ubiquitous term oblique facial cleft has also been used for this deformity. As previously stated, this term has been loosely applied to several clefts that would correspond with clefts No 3, 4, and 5 of Tessier classification.

Boo-Chai (1970) in his comprehensive review article credited the first recorded case to von Kulmus, who described the deformity in Latin in 1732. Dick (1837) reported the first case in the English literature. Most of the cases described by Morian (1887) involved stillborn infants. Boo-Chai found 23 cases in the literature involving infants who lived. Subsequently, other cases have also been reported by Tessier (1969a), Van der Linden and Borghouts (1970), Dey (1973), and Kubaček and Penkava (1974).
The location of the cleft of the lip differs from that of clefts previously described, and it is found lateral to the Cupid's bow and philtrum. The cleft rests midway between the philtral crest and the corner of the mouth. It passes lateral to the nasal ala and onto the cheek (meloschisis). The nasal ala is more or less normal. However, in unilateral cases it is often rotated toward the medial canthus of the involved side. The cleft terminates in the lower eyelid medial to the punctum. The cranial continuation of the cleft traverses the medial third of the upper eyelid and eyebrow as the No 10 cleft.

The nasolacrimal canal and the lacrimal sac are usually intact, since the cleft courses lateral to these structures. However, the lower canaliculus lies in the path of the deformity. The medial canthal tendon is almost normal in respect to its insertion and its direction (Tessier, 1969a). The eye is usually present and functional, but anophthalmia and malformations of intermediary forms can also exist (Rogalski, 1944).

On the facial skeleton the cleft is located between the lateral incisor and the cuspid, similar to the defect of the No 3 cleft. The pyriform aperture, however, remains intact. The cleft courses lateral to the pyriform aperture onto the anterior surface of the maxilla. It continues medial to the infraorbital foramen to terminate in the medial portion of the inferior orbital rim and floor. The contents of the orbit prolapse into the fissure. In depth, the fissure can extend posteriorly as a cleft of the secondary palate. The septation between the maxillary sinus and the nasal cavity remains intact. Often associated with the deformity is a posterior nasal choanal atresia. In the complete form of the cleft, the orbital cavity, the maxillary sinus, and the oral cavity are confluent. In bilateral cases, the premaxilla is in a protrusive position, and the nose appears smaller than normal.

An estimate of the distribution of the cleft can be obtained by analyzing the reports cited earlier in this section. Unfortunately, a complete description of the cases is not recorded in several of the publications. Unilateral cases totaled 27, of which 18 were located on the right side and 9 on the left side (2R:1L). In the unilateral cases, a heavy male predominance exists in a ratio of approximately 4M:1F. Seven bilaterally involved cases have been reported. In contrast to the unilateral form, the bilateral cases occurred with equal frequency in both sexes. It should be noted that six of the seven patients had a cleft of a different type on the contralateral side. On the opposite side, three patients had a transverse cleft (No 7 cleft), and the remaining three had a closely related No 5 cleft.

No 5 Cleft. Situated more laterally on the face is the No 5 cleft. The general term oblique facial cleft has again been used to designate this deformity. Karfik prefers the term true oblique facial cleft and includes the malformation in his Group E, atypical facial disorders. In the AACPR classification, the cleft is included in the oro-ocular group. In Boo-Chai's subdivision of the oro-ocular cleft group, the cleft is called type II.

Of the oblique facial clefts, the no 5 cleft is the rarest. Only six cases have been reported in the world literature (Greer, 1961; Pitanguy, 1968; Boo-Chai, 1970; Stewart, Mulick, Kawamoto, and Thanos, 1976). Tessier reported two personal cases. Among the eight cases, two are unilateral, two are bilateral, and the remaining four are combined with another rare craniofacial cleft on the contralateral side.
The cleft of the lip is positioned just medial to the corner of the mouth. It courses cephalad across the lateral portion of the cheek (meloschisis) into the area of the medial and lateral thirds of the lower eyelid. The vertical distance between the mouth and the lower eyelid is decreased, and the upper lip and lower eyelid are drawn toward each other. The eye can be microphthalmic.

The path of the skeletal malformation is also distinct. The alveolar portion of the cleft is found posterior to the cuspid in the premolar region. As pointed out by Morian, the cleft passes lateral to the infraorbital foramen, thus distinguishing it from its predecessor which is located medial to this landmark. The cleft enters the orbit through the middle third of the orbital rim and floor. The orbital contents are free to prolapse through this gap into the maxillary sinus.

**No 6 Cleft.** The incomplete form of the Treacher Collins syndrome is represented by the No 6 cleft (see Chapter 55). It is the feeling of Rogers (1964a) that the cases originally described by Treacher Collins were probably of the incomplete type.

The external features of the deformity are less pronounced and extensive when compared to those seen in the complete form. Although the external ear can be near normal or normal, a hearing deficit is often present. The antimongoloid obliquity of the palpebral fissure is milder. The coloboma of the lower eyelid is found in the usual site between the medial and lateral thirds. Inferiorly, the cleft is directed lateral to the oral commissure and toward the angle of the mandible.

It is mainly the osseous deformity that marks the cleft as a distinct entity. In contrast to the complete form, the malar bone is present but hypoplastic. The continuity of the zygomatic arch remains intact. A bony notch that corresponds to the cleft can be detected by careful palpation of the inferolateral portion of the orbital rim. The cleft is located in the region of the zygomaticomaxillary suture between the hypoplastic malar bone and the maxilla. An actual cleft of the alveolus is not seen, but a hypoplastic zone is frequently detected in the region of the molars. The antigonial angle of the mandible is accentuated.

**No 7 Cleft.** The No 7 cleft enjoys the distinction of being the least rare of the atypical craniofacial clefts. A variety of terms have been used to describe this cleft: necrotic facial dysplasia (Keith, 1940a), hemifacial microsomia and microtia (Braithwaite and Watson, 1949), otomandibular dysostosis (Franceschetti and Zwahlen, 1944), unilateral facial agenesis (Ruben, 1967), auriculobranchiogenic dysplasia (Caronni, 1971), intrauterine facial necrosis (Greer, 1961), hemignathia and microtia syndrome (Stark and Saunders, 1962), first and second branchial arch syndrome (Longacre, DeStefano, and Holmstrand, 1961), lateral facial clefts, transverse facial clefts, and oromandibuloauricular syndrome. In other classification systems, the cleft has been grouped as an oroaural cleft (AACPR) and a Group B 1 lateral otocephalic branchiogenic deformity (Karfić). The Goldenhar syndrome is closely related and has the additional features of epibulbar dermoids and vertebral anomalies (Goldenhar, 1952; Gorlin and associates, 1963). The first and second branchial arch syndrome and its variations are discussed in Chapter 54.

Ballantyne (1894) stated that the earliest recording of the malformation is in the cuneiform inscriptions on the teratologic tables written by the Chaldeans of Mesopotamia.
around 2000 BC. The first case described in a contemporary language was recorded by Reissmann (1869). Subsequently, countless articles have been written describing the deformity. Grabb (1965), in his comprehensive article, summarizes the findings of a personal series of 102 patients. Converse, Coccaro, Becker, and Wood-Smith (1973a) also reported a large personal series of 280 patients.

The statement of Gorlin and Pindborg (1964) that the male is more often affected than the female is confirmed by the statistical analysis of Grabb (1965). The side of involvement is not significant. Bilateral involvement was noted in 12 of 102 patients of Grabb, 15 of 280 cases of Converse and his associates, 8 of 74 cases of Meurman (1957), and in a 1 to 6 ratio in the series reported by Dupertuis and Musgrave (1959).

The birth incidence of the malformation is estimated to be between 1 in 3000 (Poswillo, 1974a) and 1 in 5642 births (Grabb, 1965). The vast majority of cases occur in a sporadic fashion. In the closely related Goldenhar syndrome, however, an autosomal dominant transmission is reported (Summitt, 1969). Therefore, a careful search for epibulbar dermoids and vertebral anomalies is of importance in genetic counseling.

The clinical expression of the cleft is highly variable. The forme fruste can consist of a slight facial asymmetry, minimal malformations of the external ear, and skeletal anomalies detected only on roentgenograms. Hence, even a seemingly insignificant ear tag should alert the clinician to the need for a careful examination of the child. The oral component varies from a mere broadening of the oral commissure to a complete fissure extending toward the external ear. The cleft, however, rarely extends beyond the anterior border of the masseter muscle. Further extension of the cleft can occur as a deep furrow extending horizontally across the cheek toward or around the superior aspect of the ear. The normal position of the oral commissure can often be established by the characteristic shade of the mucosa lining the cleft which is slightly lighter than that of the normal vermilion (Boo-Chai, 1969). The slightly elevated mucocutaneous ridge of the vermilion border also terminates at the normal limit of the lip.

The underdevelopment or maldevelopment of the external ear, middle ear, mandible, maxilla, zygoma, and temporal bones has been described by May (1962), Longacre, Stevens, and Holmstand (1963), Grabb (1965), Powell and Jenkins (1968), and Converse and associates (1973a) (see Chapter 54). On the cleft side, the parotid gland or its duct can be absent. The fifth and seventh cranial nerves and the muscles they serve can also be involved. The ipsilateral soft palate and tongue are often hypoplastic. Parts of the mandibular ramus and condyle and the zygomatic arch can also be absent. When the temporalis muscle is involved, corresponding changes of the coronoid process are seen. The occlusal plane is canted cephalad on the affected side, reflecting the hypoplastic maxilla and the reduced vertical height of the ramus. The skeletal malformation of the complete form of the No 7 cleft is shown. Tessier believes that the cleft is centered in the region of the zygomaticotemporal suture. The zygomatic arch is disrupted, and its remains are represented as small stumps. Lateral canthal dystopia is caused by the hypoplasia of the zygoma that results in an inferior displacement of the superolateral angle of the orbit. In the severest forms, true orbital dystopia is present.

In a report of 15 patients with bilateral facial microsomia, Converse and associates (1974) described two patients with an unusual supplementary cleft of the maxilla. In the
region of the tuberosity, a distinctly separate segment of bone with supernumerary teeth was found. Stewart, Mulick, Kawamoto, and Thanos (1976) reported two additional patients with a vertical cleft of the posterior maxilla.

**No 8 Cleft.** The No 8 cleft is seldom seen as an isolated malformation. The cleft is usually combined with another rare craniofacial cleft. The cleft corresponds to the temporal prolongation of the orolateral canthus cleft (AACPR) and the commissural clefts of the Ophthalmo-orbital disorders (Karfik).

The No 8 cleft begins at the lateral commissure of the palpebral fissure and extends into the temporal region. The lateral commissural coloboma is often occupied by a dermatocele. The osseous component of the cleft lies in the region of the frontozygomatic suture. In this location, a bony notch has also been observed by Tessier (1975) in patients with the Goldenhar syndrome.

**Combinations of Clefts No 6, 7, and 8.** When rare bilateral craniofacial clefts occur, different combinations of the various clefts are often seen. The bilateral occurrence of a combination of clefts No 6, 7, and 8 is, however, unique. Tessier (1975) felt that this group pattern of clefts best explains the complete form of the Treacher Collins (Franceschetti) syndrome. The three clefts are found in the region of the maxillozygomatic, temporozygomatic, and frontozygomatic sutures. Tessier suggested that the sum effect of the three clefts is responsible for the absence of the zygoma.

On a pre-Colombian terra-cotta statue from the seventh century, the typical Treacher Collins facies can be seen (Poswillo, 1975). Poswillo cited Thomson (1847) as being the first to describe the clinical features of the syndrome. However, Berry (1889) is generally credited with the first description of the malformation. A few years later, Treacher Collins (1900a, b) reported two cases and noted the hypoplasia of malar bones. Numerous case reports followed. Among the significant articles are those of Lockhard (1929), Franceschetti and Zwahlen (1944), Franceschetti and Klein (1949), and Rogers (1964b) (see Chapter 55).

The missing malar bone is the hallmark of the complete form of the Treacher Collins syndrome. The No 6 cleft is responsible for the coloboma of the lower eyelid. The medial two-thirds of the eyelashes of the lower eyelid is deficient or absent. Tessier (1975) stated that approximately a third of the patients do not have an infraorbital foramen. Thus, the infraorbital neurovascular bundle passes from the orbit directly into the subcutaneous tissues. The No 7 cleft explains the absence of the zygomatic arch, the fusion and hypoplasia of the masseter and temporalis muscles, the ear malformations, the anterior displacement of the sideburns, and the mandibular bony deficits. The No 8 cleft completes the malformation by contributing to the absence of the lateral orbital rim. The lateral border of the deformed orbit is often formed solely by the greater wing of the sphenoid. The lateral canthal dystopia is responsible for the characteristic antimongoloid slant of the palpebral fissures, because the lateral canthal tendon is without a point of attachment. Additional details of the syndrome are discussed in Chapter 55.

**No 9 Cleft.** Beginning with the No 9 cleft, the superior hemisphere of the orbit is involved. The clefts become the "northbound" cranial prolongations. The No 9 cleft is found in the superolateral angle of the orbit. The eyelid is divided in its lateral third.
The cleft is extremely rare. The illustration used by Tessier of this cleft is based on the descriptions of Morian (1887) and Sanvenero-Rosselli (1953).

**No 10 Cleft.** The No 10 cleft is centered in the middle third of the orbit and upper eyelid. The cleft corresponds to the cranial extension of the No 4 cleft.

A coloboma is present in the middle third of the upper eyelid. The cleft continues through the middle third of the eyebrow on its way into the hairline. The osseous structures are cleaved in the midportion of the superior orbital rim, the adjacent orbital roof, and the frontal bones. A fronto-orbital encephalocele often occupies the gap. A secondary lateral and inferior rotation of the orbit occurs. When the displacement is severe, orbital hypertelorism is produced.

**No 11 Cleft.** As an isolated deformity, the No 11 cleft has not been reported. It is usually found in combination with the "southbound" No 3 cleft of the face.

The cleft traverses the medial third of the upper eyelid and eyebrow to extend into the frontal hairline. The cleft takes one of two paths in the region of the frontal process of the maxilla when it is combined with a No 3 cleft. The first route passes lateral to the ethmoid to create a cleft in the medial third of the eyebrow and orbital rim. The alternative course is through the ethmoidal labyrinth. When this path is taken, orbital hypertelorism is produced.

**No 12 Cleft.** The No 12 cleft is the cranial equivalent of the No 2 cleft of the face. Orbital hypertelorism is usually seen. The eyebrow is disrupted just lateral to its medial border.

On the skeleton, the cleft passes through the frontal process of the maxilla or between this structure and the nasal bone. The ethmoidal labyrinth is involved and is increased in its transverse dimension to account for the associated orbital hypertelorism. The cleft is located lateral to the olfactory groove. Hence, the cribriform plate is of normal width.

**No 13 Cleft.** Changes in the cribriform plate are seen beginning with the No 13 cleft. This cleft corresponds to the cranial extension of the No 1 cleft of the face.

The hallmark of the No 13 cleft is the widening of the olfactory groove. The cribriform plate is therefore also increased in its transverse dimensions. When a paramedial frontal encephalocele is associated with the deformity, the cribriform plate can also be displaced inferiorly by the malformation.

Unilateral and bilateral forms exist as in most of the craniofacial clefts. When the cleft is bilateral, some of the most extreme degrees of orbital hypertelorism can be seen (Tessier, 1975). The ethmoidal labyrinth is expanded, and extensive pneumatization of the frontal sinus can coexist (Tessier, 1972).

On the external surface, the distinguishing sign of the No 13 cleft is the dystopia of the hair at the medial end of the eyebrow. A coloboma or notch of the eyebrow per se is not found. The medial end of the eyebrow is actually displaced inferiorly.
**No 14 Cleft.** With the No 14 cleft, the circumferential involvement of the orbit is completed. A return is made to the midline "time zone" that is shared by the No 0 cleft of the face. Similar to its facial counterpart, the No 14 cleft can be produced by agenesis of a part or an overabundance of tissue.

When agenesis is the basic theme, hypotelorism is generally seen. Included in this group of craniofacial malformations are the holoprosencephalic disorders, such as cyclopia, ethmocephaly, and cebocephaly (see Table 46-2). The cranium is usually microcephalic or occasionally trigonocephalic in shape. A total absence of the usual midline cranial base structures can occur, allowing the orbits to converge in the midline to form a solitary mass as seen in cyclopia. Malformations of the intimately related forebrain tend to be proportional to the degree of external facial disorganization. The central nervous system anomalies severely handicap the newborn, and life expectancy is usually limited from hours to several months.

At the other end of the spectrum is orbital hypertelorism associated with the No 14 cleft. Lateral displacement of the orbits can be produced by cranium bifidum or a space-occupying mass such as a frontonasal encephalocele or a median frontal encephalocele. Cohen and associates (1971b) felt that the basic embryologic fault lies in the malformation of the nasal capsule. The developing forebrain thus remains in its low-lying position. A morphokinetic arrest of the normal medial movement of the eyes occurs; the orbits remain in their widespread fetal position. The medial cranial dysrhaphia is characterized by an increased distance between the olfactory grooves. The crista galli is involved and is widened or duplicated in some cases. Occasionally the crista galli is absent (Tessier, 1975). When the crista galli is severely enlarged, preservation of the olfactory nerve is not possible. Prolapse into the enlarged ethmoidal labyrinth occurs and leads to an increase in the interorbital space and orbital divergence. Consequently, the cribriform plate, which is normally located 5 to 10 mm below the level of the orbital roof, can be caudally displaced up to 20 mm (Tessier, 1972).

The frontal bone is flattened, giving the glabella an indistinct appearance. When an encephalocele is present, large defects of the frontal bone are often seen. In a roentgenographic study, Brejcha and Fára (1971) found an absence or an atypical pneumatization of the frontal bone.

**Treatment**

From the foregoing descriptions, it is evident that each craniofacial malformation is unique. The planning of corrective procedures cannot be standardized. Nevertheless, certain general principles can be outlined in the sequence and execution of the operative stages.

In general, the age at which repair is initiated varies with the severity of the deformity. Treatment of the milder clefts, not significantly interfering with function, is not urgent. The use of suitable delay takes advantage of the rapid growth of infancy. Growth appreciably increases the size of the component structures, facilitating repair and allowing accuracy of approximation. By contrast, in severe deformities that impose physiologic hazards, the initial repair should commence as soon as the infant has adjusted to his environment and has regained his birth weight. In these cases, early reconstructive surgery improves function and
assists in achieving a more normal positioning of the skeletal structures by the molding and splinting effects of the repaired soft tissues.

The extent of operative intervention in early childhood generally should be limited to the soft tissues. Interference with normal growth patterns can be produced by ill-timed operative trauma on the deformed bony structures. The growth potential and subsequent change in the deformity of the skeletal framework are unpredictable at this time. However, patients with severe clefts and hypoplasia of the craniofacial skeleton pose a dilemma, since only limited bony growth is expected.

Clefts of the soft tissue generally involve all layers. Any scar interposed within the fissure should be excised to a width necessary to expose normal tissue. Repair of the cleft must include accurate approximation of each individual layer. Failure to obtain meticulous layer closure will result in a loss of anatomical continuity and a depression along the site of the operative repair. When the repair crosses the lines of minimal tension or when there is a loss in length, multiple Z-plasties can be used to advantage.

The esthetic demands of a well-performed repair of the soft tissue deformity cannot be denied. However, the reconstruction of the supporting skeletal framework is equally important. An appreciation and understanding of the skeletal malformation is basic to any reconstructive procedure. Without proper osseous support, the soft tissue correction that appears to be satisfactory at the time of closure is doomed to a less than ideal long-term result.

In addition to the general principles outlined, specific problems arise in relation to the individual clefts.

In the median cleft of the upper lip, repair of the soft tissues of the lip is achieved in layers, with particular attention to accurate alignment of the vermilion border and coaptation of the reoriented muscle layer. When the cleft extends through an appreciable height into the philtrum, a zigzag form of closure may be preferred to prevent possible linear contracture of the scar and subsequent notching of the lip. Duplication of the frenulum is usually not of functional significance and does not require specific repair. However, the frenulum should be excised if it extends well onto the alveolar ridge to produce a diastema between the central incisors. Malposition of the upper central incisors is corrected by orthodontic therapy. Absence of or rudimentary development of the premaxilla creates an instability of the entire maxillary arch. A crossbite is produced as the maxillary segments collapse toward the midline. Protractive orthodontic treatment and bone grafts are often necessary for correction. As an adjunct to orthodontic expansion, a horizontal cortical osteotomy in the region of the zygomaticomaxillary buttress will expedite the process. Surgical correction of the bifid nose and the hypertelorism is reviewed in Chapter 56.

In the median clefts of the lower lip, problems encountered in handling the soft tissue defects are essentially similar to those outlined for the upper lip. A simple V-excision of the cleft with closure in layers can be performed. A step closure, staggering the mucocutaneous junction (Millard, Lehman, Deane, and Garst, 1971), can also be used to prevent notching of the vermilion border. When the tongue is bifid, it is held in an abnormally anterior position
by a short frenulum that limits lingual mobility. Lengthening the frenulum is indicated to free the tongue, and a Z-plasty is a satisfactory procedure for this purpose.

Complete clefts of the mandibular symphysis should not be corrected in infancy. Success is unlikely in the uncooperative child without stabilization by intermaxillary fixation. Malalignment of the dental arches is always present when the mandible is cleft. Normal interarch relationships cannot be improved by direct approximation of the bone ends, since an actual loss of tissue is involved (Ecker, 1958). The gap can be as great as 3 cm. Restoration of continuity, therefore, requires the insertion of a bone graft.

Midline fibrous web contractures of the anterior neck region require early correction to permit adequate growth of the mandible and to restore the cervicomental angle. Simple excision of the contracted fibrous cords of the anterior ribbon muscles fails to provide a permanent cure (Davis, 1950). A Z-plasty is often required (Monroe, 1966) to prevent recurrent contracture. On occasion, introduction of additional soft tissue to the involved area by means of a skin flap is needed.

The management of a case of partial duplication of the midfacial structures by Calaycay and his associates (1976) illustrates what can be achieved by a well-planned, staged approach to an unusual complex malformation. At the age of 2 weeks, after the newborn had adjusted to its new environment, transection of the oral mass that separated the maxilla from the mandible was performed under local anesthesia to improve the airway. A gastrostomy was also provided for feeding purposes. During the 16th week of life, the entire oral mass with its intermaxillary bony struts was removed under general anesthesia. The second operation also included a palatoplasty and an attempted repair of the cleft of the upper lip. Unfortunately a dehiscence of the cheiloplasty occurred. When the infant was 9 months old, the bifid tongue was corrected by a Z-plasty, and the redundant portion of the lower lip was excised. Three months later, the lower third of the nose was corrected, and a secondary palatoplasty and upper lip repair was performed.

The No 3 cleft (naso-ocular) represents one of the most difficult and challenging malformations for the reconstructive surgeon. The decreased vertical dimension between the ala and the medial canthus is corrected by a Z-plasty (Tessier, 196a, b). The restoration of the vertical distance of skin by the local skin flap is accomplished at the expense of the width. Tessier emphasized the need for wide undermining of the soft tissue over the maxilla and the zygomatic arch to achieve tension-free soft tissue coverage. Bone grafts are used to support the prolapsed contents of the orbital cavity and to fill the defects of the skeleton. Lining is obtained from the mucosa of the nasal floor or septum. The nasal lacrimal system is disrupted by the cleft malformation; the nasolacrimal duct is blocked, and the sac is prone to repeated infections (Gunter, 1963); the lower canaliculus is malformed and beyond repair (Tessier, 1969a). Total extirpation of the sac and duct remnants is, therefore, the treatment of choice. Because the medial canthal tendon is hypoplastic and its insertion is inferiorly displaced, it cannot be relied upon for the medial canthopexy. Transnasal wiring must be used to reposition the medial canthus. An urgent situation exists when the eye is normal but is unprotected because of the coloboma. Early repair of the coloboma is imperative to prevent corneal ulceration and serious impairment of vision. When microphthalmos is present, the problem of restoring facial symmetry is compounded.
The No 4 cleft spares the nose and the pyriform aperture. The decrease in vertical dimension occurs between the mouth and the medial third of the lower eyelid. Restoration of soft tissue continuity is achieved with the use of local interdigitating flaps (Tessier, 1969a, b). The nasolacrimal canal and lacrimal sac lie medial to the cleft; the lower canaliculus, however, is disturbed. The medial canthal tendon is almost normal in respect to its direction and insertion (Tessier, 1969a). Thus the medial canthal tendon stump can be used when performing a canthopexy. Bone grafts are required to correct the orbital dystopia by rebuilding the orbital rim, orbital floor, and maxilla.

Treatment of the No 5 cleft is similar to that of the No 4 cleft. Interlocking small triangular flaps are used to repair the soft tissue cleft (Boo-Chai, 1970). Bone grafts are again employed to restore the underlying skeletal support.

Correction of clefts No 6, 7, and 8 associated with the Treacher Collins syndrome is discussed in Chapter 55. There is little disagreement that the soft tissue gaps that are associated with the No 7 cleft should be corrected early. The repair is relatively simple when only the soft tissue is involved. After excision of the margins of the cleft, the soft tissue is approximated in layers. The separated muscles are identified and carefully approximated. The principle of reorientation and approximation of muscle is also applied in reconstituting the orbicularis oris muscle in the reconstruction of the commissure of the mouth. The achievement of symmetry is essential. When the cleft is unilateral, the normal commissure is used as a guide to determine the exact location of the reconstructed commissure. In the case of the bilateral cleft, the site of the future commissure is determined by locating the transition point between the mucosa of the red lip and the deeper hue of the buccal mucosa (Boo-Chai, 1969). The actual reconstruction of the commissure is achieved by the use of a simple Z-plasty (Longacre, DeStefano, and Holmstrand, 1961) or a small Estlander flap from the lower lip rotated superiorly to the upper lip (May, 1962). The pedicle becomes the reconstituted commissure. Another method is to construct a broad mucosal vermillion flap along the border of the cleft. The pedicle is based on one lip at the site of the future commissure and is rotated past the reconstructed commissure to be inserted into the prepared recipient site of the opposite lip (Stark and Saunders, 1962). The slight "dip in" of the normal commissure can be reproduced by utilizing a small triangular flap. The skin flap is based laterally and is transferred inward with its tip sutured to the mucous membrane lining just inside the commissure. This Y-V procedure is used as a second stage procedure when a mucosal pedicle has been used to form the commissure during the primary repair (see Chapter 32). Mansfield and Herber (1972) suggested the use of a large Z-plasty that transposes the soft tissues of the neck into the depressed area of the lower face.

Correction of the soft tissue deformities of the Treacher Collins syndrome depends a great deal upon the restoration of the bony architecture (see Chapter 55). It should be recalled that approximately a third of the patients do not have an infraorbital foramen (Tessier, 19750. In these patients, the infraorbital neurovascular bundle passes from the orbit directly into the subcutaneous tissues. Care must therefore be exercised when the dissection is performed in this area.

When should reconstructive surgery of the facial skeleton begin? There is disagreement surrounding this question. Proponents of early intervention argue that the psychologic consequence of the deformity is less and that early surgery encourages rather than interferes
with any growth potential. Although they acknowledge the detrimental psychologic implications, opponents of early osseous reconstruction feel that surgery interferes with any remaining growth potential.

In the case of the No 7 cleft (hemicraniofacial microsomia), Brown, Fryer, and Ohlwiler (1960), Longacre, DeStefano, and Holmstrand (1961) and Stark and Saunders (1962) favor early correction of the problem and have advocated the use of inorganic implants, autogenous cartilage, and bone. Converse and associates (1973b) combined the early use of mandibular osteotomies and orthodontic therapy and have published a series of long-term results. Balancing the early intervention school is the clinical work of Obwegeser (1970, 1974) and the experimental findings of Poswillo (1974b). After the facial skeleton has ceased to increase in size, Obwegeser employs onlay bone grafts to rebuild the deficient skeletal contour, together with sagittal-split osteotomies of the mandible and a Le Fort I osteotomy of the maxilla. In animal studies, Poswillo found that hemorrhage in the otomandibular region destroys the developing muscles, ligaments, and bones. The functional matrix (Moss, 1968) thought to be required for growth is obliterated. Thus Poswillo concluded that the results of early reconstructive surgery would be short-lived.

On the other hand, in treating the Treacher Collins deformity (clefts No 6, 7, and 8), Poswillo felt that early intervention is indicated. Based on his animal investigations, Poswillo suggested that "a degree of functional autonomy sufficient to provide growth of the facial skeleton" is preserved and that the principal deficiency is in the amount of mesenchyme that forms the facial skeleton. Correction of this deficit would restore the functional matrix. The clinical observations of Tessier (1975), however, showed that what is theoretically possible is not often achieved in daily practice. Following many patients on whom an early operation was performed, Tessier noted that the malformation has an insatiable appetite for bone grafts. Consequently, correction of the skeletal malformation is postponed until adolescence, at which time the resorption of the bone grafts is appreciably less.

Beginning with the No 9 cleft, the cranium itself becomes involved. Depending upon the severity of the deformity, an intracranial or extracranial approach is used. The indications and the surgical techniques of these operations are discussed in Chapters 27 and 56.