Converse: Chapter 39

EMBRYOLOGY OF CLEFT LIP AND PALATE

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The embryologic development of the face has always presented the physician and scientist with an enigmatic mosaic so very different from those satisfying blocks of mesoderm, the somites, which will, with replicating exactitude, form bone, cartilage, muscle, nerve, and blood vessels through the embryo's length. For the sake of simplifying facial development in the embryo, the concepts of developing gill systems and of tentacled, fingerlike processes have been introduced as a sort of literary analogy, much as the reduplication of somites in the human embryo has been compared to the action of the metameres of the earthworm. These homologues have been borrowed from families and orders lower than homo sapiens. The concept of fusing processes has been borrowed from the chick, pig, rabbit, and deer by the Swiss Wilhelm His (1831-1904), and those of the gill or branchial arches from the fish by the Scot Francis Maitland Balfour (1851-1882).

This comparative embryology, termed the theory of recapitulation, was in vogue in the last half of the nineteenth century. However, in the twentieth century, the American embryologist George L. Streeter emphasized the utter futility of interpreting development in all orders, families, genera and species in the simplistic terms of the embryology of the chick or of the frog.

The classical doctrine of Wilhelm His (1874) concerning the formation of the central third of the face stated that the "mid-portion is occupied by the oral cavity which is remarkably wide and angular; the lateral borders are formed by two maxillary processes. Above the mouth, the large expanse of the frontal process is found. Two clefts originate from the mouth on each side and end as blind pits. The first of these is the nasal cleft, which runs up into the frontal process to form the olfactory pit. The second cleft lies between the frontal process and the maxillary processes and ends up at the lens placode to become the naso-optic furrow. The naso-optic furrow remains open for some time, but eventually closes to form the nasolacrimal duct".

The doctrine of Wilhelm His has persisted to modern times, so that Arey (1947) explained cleft lip as failure of "fusion of the median nasal and maxillary processes". Furthermore, Patten (1961) stated, "It is quite obvious that such a (cleft) lip is located at the line where, during the second month of development, the maxillary process should have fused with the naso-medial process".

The concept that fusion of fingerlike processes would obliterate de novo lip clefts and thus result in normal development of the central face and, conversely, that fusion interrupted by" arrested development" would cause the original cleft to persist until birth has undergone increased scrutiny during the past 30 years.

Two concepts have been challenged: First, the preexistence of clefts of the lip, and second, the view that clefts are due to "arrested development". There is a body of opinion that the clefts described truly represents furrows. This has been a difficult dilemma to resolve,

since the head is flexed and the face is in apposition with the developing heart. Another body of opinion feels that a cleft develops because the lip anlage or primordium has been incompletely reinforced by mesoderm, resulting in rupture.

Victor Veau expressed doubt about the "arrested development - persistent cleft" theory (1931). He felt, after viewing Hochstetter's two embryos, that a Simonart's band in one suggested that the lip was fraying, indeed was being pulled apart, rather than processes had met and were beginning to fuse, and that the cleft was the result of a traction, not a pulsion, force. In 1948, Streeter suggested that initially the upper lip was an epithelial structure without clefts which would develop normally only if mesoderm reinforced the furrows present under either nostril.

In five cleft lip human embryos, Stark in 1954 made quantitative measurements of the mesoderm on the normal versus the cleft side of the lip, showiung that mesoderm is absent on the abnormal side. Johnson (1965) provided additional evidence by radioautographic studies of dynamic mesodermal migration from the dorsal perivertebral region over and around the head to reinforce the face.

Mesodermal Reinforcement of Branchial Membranes

The following conceptual sequence of events has been formed from this study: The oral dimple pushes ectoderm into the mouth where it lines the oral plate (stomodeum) on one side, while entoderm of the primitive gut lines the other side near the diverticulum (Seessel's pocket). With the formation of the oral dimple or pit, the upper lip exists originally as a bilamellar branchial membrane, both laminae consisting of ectoderm; this is the "epithelial wall" of Hochstetter and Veau.

This two-layered gossamer branchial membrane is one of many which exist in embryonic life, although only a few (tympanic membrane, vaginal hymen) persist unti birth. The great majority rupture, unable to withstand the pressures of growth. Branchial membranes represent transient bilamellar structures ordinarily destined to be reinforced and filled out by mesoderm in the first three months of embryonic and fetal life, the period of organogenesis. The membrane or epithelial wall will ordinarily be reinforced by mesoderm that migrates around both sides of the head, as well as over it.

In the area of the "epithelial wall", mesoderm, which will form bone, cartilage, muscle, nerve, blood vessels, and lymphatics, will migrate into three predetermined loci. As it moves laterally around the head, mesoderm will make a deposit on either side of the upper lip. A third deposit will move over the top of the head to reinforce the center of the lip. The latter deposit is subdivided into two parts or lobes.

Other predictable deposits are made in the normal head and face. Failure of mesodermal delivery from the migratory route over the head will result in forebrain maldevelopment or arhinencephaly, in which at the least the olfactory lobes are deficient and there will be an associated medial cleft of the lip. Mesodermal deficiency in the malar region will produce Treacher-Collins syndrome; in the area of the first branchial arch, the syndrome of macrostomia, hemignathia, and preauricular tags; in the area of second branchial arch,

maldevelopment of the ear and facial palsy; in the area of both the first and second branchial arches, microtia; and in the neck, cervical fistula.

In other areas, mesodermal reinforcement of branchial membranes is necessary - for example, if the heart is to be covered with an intact thorax and not exposed as in ectopia cordis; if the abdominal wall is to envelop the gastrointestinal tract and not expose the gut, as in gastroschisis; and if the bladder is not to lie atop the abdominal wall, as in exstrophy of the bladder.

When an insufficient deposit of mesoderm is made, the unreinforced bilamellar branchial membrane splits apart. The reinforcement may fail totally, hence rupture is complete. On the other hand, the membrane may be partially reinforced, so damage is not total and only a partial rupture occurs. And alternatively, the mesoderm programmed to arrive on schedule may arrive to late; membrane rupture may exist in the presence of separate cleft elements that are fully developed.

In the anlage of the upper lip, mesoderm is delivered according to a chronologic schedule of priorities; first in the neighborhood of the incisive foramen, then in the nostril floor, next the nostril sill, the upper part of the lip, and lastly the vermilion. If, in the lip, delivery fails totally, a complete or total rupture of the epithelial wall will occur, and the infant will be born with a cleft extending all the way back to the incisive foramen. If the lateral delivery fails on both sides, a bilateral complete cleft will form. If the delivery failure is central, the infant will be born with arhinencephaly and a median cleft lip.

As mentioned, the mesodermal delivery may be in short supply. If minimally deficient, the resulting defect will also be minimal - a notched vermilion, a subcutaneous lip furrow, or a "cleft lip nostril" without signs of a cleft lip. If, however, the amount of mesoderm delivered lies between total absence and the most minimal, the first mesoderm to arrive will close up the nostril floor from the incisive foramen outward to the nostril sill. Then if additional mesoderm arrives, it will reinforce the lip from the nostril down to the vermilion.

Polarization of Ectodermal Cell Masses

Thus far, the only mechanism mentioned in orhanogenesis has been mesodermal reinforcement of branchial membranes. Two other mechanisms are active, each contributing to normal organogenesis. The first consists of ectodermal sculpting, a mechanism in which ectodermal cells proliferate, move into an area, then carve furrows or dig cavities and tunnels. To accomplish this, cells polarize - line up in one plane - and those nearest the basement membrane are nourished by transudate; those farthest from the source of nourishment die and are shed. By this mechanism, the embryo develops nostrils, converts the limb bud cum spatula into a hand with digits, and changes the vagina from a core of solid cells into a cavity.

Once mesoderm has been delivered to the area of the upper lip, two paired arches of ectoderm appear as the primitive nose. Ectoderm proliferates and in the area of the future nares moves posterior; a basement membrane forms. Cells align and those lying distant from it are shed. In this way the twin nasal fossae burrow more deeply, eventually breaking through mesenchyma and mesoderm into the oral cavity. The final rupture breaks the oronasal membrane. The twin tunnels, the nasal fossae, have circumscribed the area of mesoderm that

will produce the prolabium, the premaxilla with four incisor teeth, the anterior nasal septum, and the columella.

Once the essential mesoderm has been deposited in the above area, refinements other than formation of the nostrils occur. After the seventh week the dental lamina appears. This is a semicircular band of expanding, polarized ectodermal cells which is to sculpt the alveolar-labial sulcus, the groove between the lip and gum. After the fundamental primary palate is formed, additional late-arriving mesoderm migrates from each lateral side to pile up in the center of the prolabium, forming the parallel philtral ridges, with the intervening philtral groove and dimple.

In the event that the primary palate pulls apart, neither the dental lamina nor the philtrum will form, simply because the late-arriving ectoderm and mesoderm cannot bridge the crevasse. That is why in complete bilateral cleft of the primary palate, the intermaxilla, the combined prolabium and premaxilla, will not receive the refinements of the alveolar-labial sulcus or of the philtrum.

Classification and Nomenclature

The area circumscribed by the paired nasal fossae produces more than the lip. It produces the premaxilla - the keystone to the dental arch with its four teeth - the caudal nasal septum, and the columella, and it is patently inadequate to speak of a cleft of this area as a "cleft lip". The term is simply not sufficiently inclusive.

The dilemma over naming this area, if we do not cal it "lip", has been resolved in favor of the embryologic term "primary palate", implying that the development of this area of palate (from four to seven weeks) precedes in time the development of the "secondary palate", the hard and soft palate which is formed from seven to twelve weeks.

In 1958, in collaboration with Kernahan, the author proposed a new classification for facial clefts based upon the embryologic findings that have been discussed thus far. Whereas older classifications recognized that the "lip" developed in a different manner and at a different time from the "palate", the anatomical division between the two structures was thought to be the alveolus. In the above classification it was proposed that the incisive foramen, not the alveolus, embryologically divided the two types of embryogenesis and the two types of deformities. With embryology thus aiding nosology, it became a simple matter to assign that hitherto unclassifiable anomaly - the bilateral cleft of the lip and alveolus, with the palate intact posterior to the incisive foramen - as a bilateral complete cleft of the primary palate. At the Rome Congress of the International Confederation of Plastic Surgery in 1967, the classification was adopted as the official one.

The classification divides the primary palate, the lip and premaxilla, which develop from four to seven weeks by mesodermal reinforcement of branchial membranes and by polarization of ectoderm, from the secondary palate, developed from seven to twelve weeks by positional change of palatal processes which grow, meet, and fuse, at the incisive foramen.

Clefts of the primary palate may be complete (cleft as far posterior as the incisive foramen) or incomplete (cleft not as far posterior as the incisive foramen); they may be

unilateral, bilateral, or median. In a complete median cleft, the intermaxilla - prolabium and premaxilla - would be absent; in an incomplete cleft, the intermaxilla would be minuscule.

Clefts of the secondary palate may be complete (cleft as far anterior as the incisive foramen) or incomplete (cleft not as far anterior as the incisive foramen). An additional form of a cleft of the secondary palate exists wherein the roof of the mouth is ostensibly normal, yet there is a palpable notch where the palatine bone should be fused, and a diastasis of the musculature of the velum exists. Often the uvula is distorted. This anomaly of the secondary palate is termed a submucous cleft.

Combined clefts of the primary and secondary palate coexist and imply prolonged exposure of the developing embryo to a teratogenic influence. There may be unilateral, bilateral, or median clefts of the primary palate combined with clefts of the secondary palate; the clefts may be incomplete or complete.

Positional Change, Growth, and Fusion of Palatal Processes

The third embryologic mechanism essential to normal development is the formation of a bridge. Here two processes form and sometimes change position, yet they always grow toward one another, then meet, adhere, and meld. This is the mechanism by which the nasoptic furrow is converted into the nasolacrimal duct, by which the penile urethra develops in the male and by which the roof of the mouth is formed.

At the seventh week, after the primary palate has formed, the palatal processes, which *do* exist in the secondary palate, hang vertically diownward alongside the tongue. The head, which has been flexed and turned to the right, now begins to extend. As it does so, the tongue begins to drop, first at its base in the pharynx. This mechanism allows the palatal shelves in that area to rise above the tongue. As the tongue drops in its midportion and then anteriorly, the shelves snap up from back to front in a movement that has been likened to the rolling of a wave. Burdi and Silvey (1969) have shown that in the male the palatal shelves have assumed the horzontal position by the seventh week, while shelves in the female are not horizontal until the middle of the eight week. This implies that in the female, the secondary palate is open longer than in the male, hence longer susceptible to any teratogenic influences. This delay could possibly explain the greater incidence of secondary palatal clefts in females. Complete clefts of the secondary palate are twice as common in the female as in the male, and clefts of the velum are 1.2 times more common.

Once the palatal shelves are in the horizontal position, they grow toward the midline and meet first at the anterior third of the hard palate. Contact continues up to the incisive foramen and then posteriorly as far as the uvula. A marginal tackiness seals together the two shelf edges. Consolidation of the contact occurs as mesoderm merges, one side with the other, and the intervening epithelial cells die.

Embryologic Formation of the Nose

One stigma of a cleft of the primary palate which is usually corrected with less finesse than the lip is the coexistent nasal distortion. There has remained the mystery as to whether the nose is asymmetric because the cleft half is displaced or whether a discrepancy in size

exists between the two halves. Is the nasal deformity due to displacement of the cleft half as the alar base sinks into the crevasse, or is it due to an inherent tissue deficiency on the side of the malformation? Huffman and Lierle (1949), studying adults with facial clefts, felt the deformity was due to malposition of the cleft half of the nose and not to a difference in size, although they made no quantitative measurements.

The single consistent finding by the author in the measurement of ectodermal volume on the two sides of the primitive nose in embryos with a unilateral defect was the relative deficiency on the side of the cleft. In the smallest embryo (24.5 mm), the ectodermal ratio between the normal and the cleft side of the nose was 6.1 to 5.4 cm^2 or a deficiency of 7 mm^2 on the side of the cleft. In the middle-sized embryo (36 mm), the ratio was 23.4 to 20.2 cm^2 or a deficiency of 32 mm^2. In the largest embryo (48 mm), the ratio was 18.2 to 14.8 cm^2 or a deficiency of 34 mm^2. These smaller measurements compared with those of the smaller embryo previously mentioned underscore the fact that some individuals are destined to have large noses, and some to have small noses.

The startling primordial nasal deficiency in the bilateral cleft has always loomed subliminally large in the minds of plastic surgeons, who must produce an acceptable nose in the absence of a columella; it has loomed as an unseen but always insurmountable spectre. The deficiency of nasal germ plasm is in large measure responsible for the truth of the statement of Brown, McDowell and Byars (1947) that, "The surgical repair of double cleft lip is about twice as difficult as in single clefts and the results are only about half as good".

In this embryologic study, the manner in which ectoderm sculpts the normal embryo was striking, as seen in the formation of the normal nasal fossae and of the normal oral sulci through its intermediary, the dental lamina. However, if no mesoderm reinforces the nostril floor, the same epithelial plug that will form the nasal fossa on the normal side appears in the side bereft of mesoderm, foreshadowing cell death and rupture of the branchial membrane. If rupture is not complete, the plug remains as a Simonart's band.

Consequently, the epithelial wall, unreinforced by mesoderm, is prey to a cannibalistic sculpting of ectoderm, which burrows into the wall, attenuating it and finally severing the wall.

In summary, part of the mechanism of rupture of the epithelial wall is rapid growth, which produces sufficient traction to pull apart the unreinforced wall. Part is also due to the burrowing ectodermal rodent, which accomplishes the final coup de grace. In no way, as claimed by His, is this a failure of fusion due to "arrested development".