I. Basics

1. *Embryological Theories*

THE embryological development of the face is still somewhat of a mystery. From the scant evidence we have, it is impossible to determine exactly how clefts form. It is like trying to re-create an intricate and technical full-length movie from a few one-frame film scraps cut at random out of the reel. There seem to be a number of intriguing theories, each of which has some evidence in its favor.

FUSION OF PROCESSES

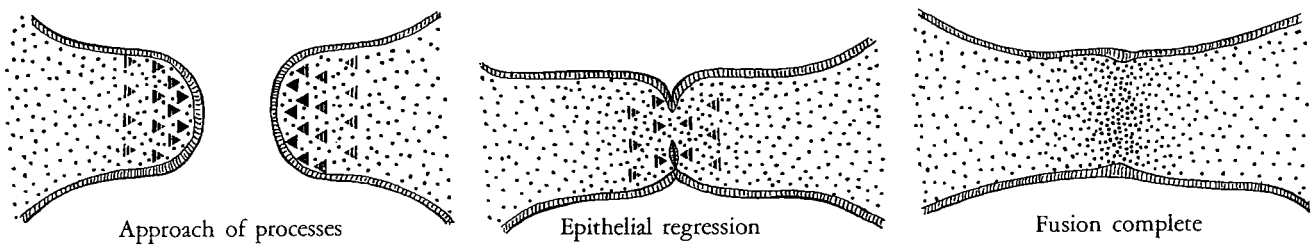
The theory that separate processes fuse to form the central face was first advanced by Meckel in 1808 and later supported by Baer in 1828, Rathke in 1832, Kölliker in 1860 and Kollmann in 1868. German anatomist Dursy in 1869 and German biologist Wilhelm His of Leipzig University in 1901, working on chick embryos, popularized the theory of embryological development of the mid-face by the fusion of five facial processes about the rim of the primitive oral cavity or stomodeum. Superiorly there is the frontonasal process; laterally there are the paired maxillary processes and inferiorly the paired mandibular processes. According to the classical theory, all of these processes grow forward as finger-like projections to fuse with each other to form the normal face between the fifth and eighth weeks. The frontonasal process gives rise to three processes, the frontal, nasomedial (globular) and nasolateral, responsible for the development of nose, prolabium and premaxilla. The maxillary process by fusing with the nasomedial process forms the lateral upper lip and

Wilhelm His

cheek. The mandibular processes meet to form the lower jaw, chin and lower lip. This hypothesis reigned some 30 years as the accepted basis of facial formation. The failure of fusion of these processes seemed to explain the formation of the various degrees of unilateral and bilateral clefts and even the rare midline upper and lower lip cleft.

Thomas Mullen of San Francisco in 1931, following the Dursy-His hypothesis, described it this way:

> Embryologically the growth toward the median line of the processes going into the formation of the mouth and lips, progresses, until in the seventh week they have fused. The manner in which the processes unite is similar to the healing of wounds. The ectodermic coverings of the processes unite and the mesodermic elements spread across the line of epithelial union to give rise to the muscles and connective tissue of the adult structure. Epithelial ingrowths separate the lips from the alveolar portion of the jaw.



Thirty years later Patten, for Pruzansky's 1961 book *Congenital Anomalies of the Face and Associated Structures,* presented this schematic design of the fusion hypothesis.

The fusion theory is no longer in vogue. The term "process" implies a finger-like projection of tissue, and "fusion" implies that the projections meet, their epithelial walls disappear and they then grow together. As shown as early as 1910 by Pohlmann, this is not the case. Inspired by Fleischmann, Pohlmann was the first to cast doubt on the classical theory, realizing it was not a question of separate processes but of localized prominences.

MIGRATION OF MESODERM

Zoology professor A. Fleischmann of Erlangen, Germany, in 1910 had a hypothesis that

cleft palate is the arrest of the disappearance of the epithelial membrane which remains intact, not penetrated by the adjacent mesoderm.

This mesodermal penetration theory appealed to Victor Veau, who admitted that until 1930, at the age of 60, he had never even looked at an embryo. As he wrote in 1935:

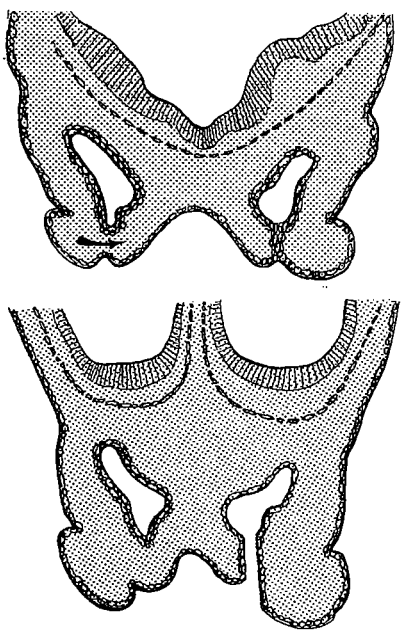
I was searching for an operative method for the treatment of cleft lip. . . . I ascertained the fact that the only productive methods were those which approximated normal development: surgery of malformations is experimental biology. . . . The theory of the coalescence of the processes led me to a method that I thought to be a good one because it had an embryological basis. I experienced a series of disasters.

In 1934 Veau, disenchanted with the old facial process theory which he now considered a "myth," sent data obtained from Fleischmann to Professor Hochstetter of Vienna. Hochstetter had been the first to describe the oronasal membrane, an incomprehensible finding according to the theory of facial processes. Hochstetter answered Veau by sending him two embryo specimens that had been puzzling him for some time: a 22 mm. unilateral cleft and a 23.3 mm. bilateral cleft. Veau was ecstatic:

You can imagine how joyful I was. . . . I found the undisputable proof of the Fleischmann theory.

Veau, the surgeon, noted in 1935:

I have been the gardener who has been responsible for the growth of the small plant, once it was germinated. The embryologists ignored Fleischmann or only referred to his hypothesis with irony. I showed that his theory could be applied to all clinical varieties of the cleft lip malformation.



Thus Veau endorsed the theory that with the penetration of mesoderm across the groove (*arrow*) normal development ensued while failure of the mesodermal migration eventually led to breakdown and cleft formation.

It is of interest that, although Veau changed his embryological ideas, this switch did not greatly influence his treatment of clefts. His acceptance of the importance of mesodermal penetration might, however, explain his enthusiasm for wire approximation of the muscles across the cleft.

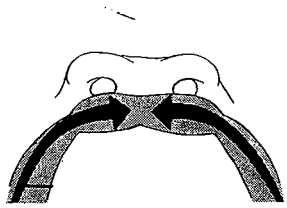
MORE EMBRYOS

Richard Stark

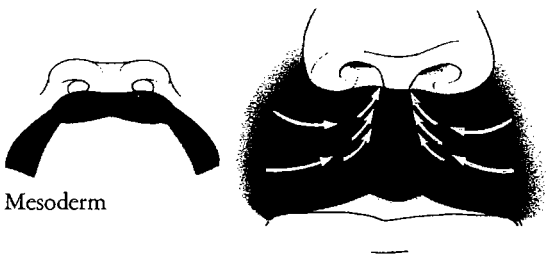
Studious Richard B. Stark of St. Luke's Hospital, New York, with access to several more embryos with clefts, probed the mysteries of cleft formation and, like Veau, came up enthusiastic about the mesodermal migration hypothesis. He has written much on this subject, beginning in 1954 and including his presentation at the 1971 Melbourne congress, but extracts from his personal correspondence in 1972 are most pertinent. He outlined the pathogenesis of facial clefts during the first four to seven weeks:

As the discoid embryo develops a head and tail fold, so too does it develop an oral dimple, a two-layered stomodeal plate, composed of oral cavity ectoderm and entoderm of the primitive gut. The bilamellar membrane that forms in the region of the upper lip consists of two layers of ectoderm called an "epithelial wall" by Hochstetter.

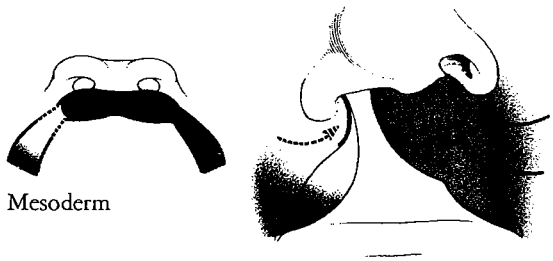
If these gossamer two-layered membranes are not bolstered early, rapid embryonic growth dooms them to rupture with the production of a cleft. . . .



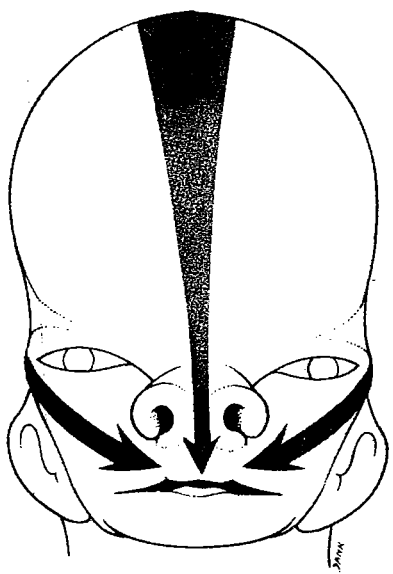
Mesoderm



Mesoderm



Mesoderm

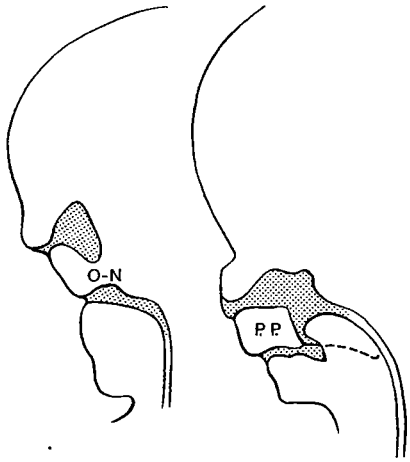


In the head and neck regions, mesoderm migrates over as well as around the head. Migration *over* the head is necessary if the forebrain, nasal dorsum and the central lip are to develop normally. Migrating around the head bilaterally, mesoderm reinforces the "epithelial wall," the branchial membrane of the lip, first posteriorly near the future incisive foramen. As more mesoderm migrates medially, it forms the nasal floor as far as the nostril sill and reinforces the alveolabial complex, then the lip and finally the vermilion.

Mesoderm does not always arrive in sufficient amount to prevent the unreinforced membrane from splitting apart. If reinforcement fails totally, the result is a complete cleft whereas if the mesoderm is only partially present there will be a partial cleft. If the mesoderm arrives too late for effective reinforcement the anomaly will exist as separated but fully developed parts.

While the primitive nose takes form as two nasal placodes, inverted

ectodermal horseshoes, it is reinforced with mesoderm in the region of the nostril floor. The ectodermal cells involved begin to proliferate carving furrows and sulci and digging cavities and tunnels to create nostrils and alveolabial sulci. Deeper burrowing extends the twin nasal fossae through the mesenchyme and mesoderm into the oral cavity with a double tunneling "break-through" which actually circumscribes the mesoderm of the prolabium, premaxilla, anterior nasal septum and columella of the *primary palate* (P.P.). All this occurs from the 4th to the 7th week. After the 7th week the dental lamina appears and late-arriving mesoderm migrates into the prolabium piling up on either side as philtrum ridges.



Richard Stark and Joshua Kaplan in 1973 attributed insufficient mesoderm migration into the lip and nasal floor as the basic cause of cleft formation and the absence of dental lamina and the philtrum in the area of the cleft. They also tag part of the blame on

mesoderm, Too little or too late

> the cannibalistic sculpting of ectoderm burrowing into the wall, attenuating it, fraying it, finally severing it. . .

and the tension of rapid growth causing traction to the point of rupture. In an incomplete cleft it is their opinion that the epithelial plug has remained as Simonart's band.

The area of lip and palate clefting has been divided into two major parts with the incisive foramen as the demarcation point.

1. The *primary palate,* consisting of the anterior nasal spine, columella, medial portion of the upper lip and premaxilla, develops during the fourth to seventh week of intra-uterine life.
2. The *secondary palate,* consisting of the hard and soft palate, develops during the seventh to twelfth week of intra-uterine life.

Division of the primary and secondary palate is marked by the incisive foramen in the roof of the mouth and bilateral sutures which extend from this midline foramen to the space between the maxillary lateral incisor and first canine tooth.

A SIMPLIFICATION

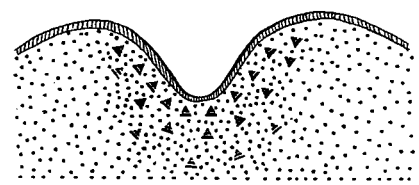
Quite simply the mesodermal migration theory proposes that coincidental with invagination of the oral cavity and nasal pits

there is a "heaping up" of the adjacent tissue forming facial prominences. As the oral and nasal cavities deepen, there is an increase in the sizes of these prominences due to the penetration of mesoderm. As more mesoderm enters the area, the bulging effect is increased so that what used to be a wall of tissue with ectoderm on one side and endoderm on the other is transformed into a conglomerate of hills and valleys. The difference between a "hill" and a "valley," or a prominence and an apparent groove, is merely dependent on the amount of mesoderm between the two epithelial layers. As these prominences approach each other, their blending is at the expense of the "valleys" or grooves, and the normal facial contour evolves. Failure of sufficient mesoderm to migrate into a specific area would be responsible for the persistence of a groove. With consequent epithelial breakdown, the persistent groove gives way to an established cleft.

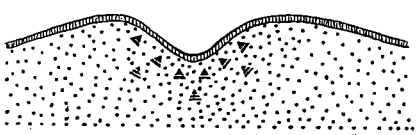
Bradley Patten

A MERGING

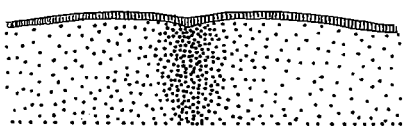
Bradley M. Patten, Emeritus Professor of Anatomy at the University of Michigan, was the son of a professor of anthropology at Dartmouth College, and throughout his life there was always a bit of the Ivy League about him. He combined the Dursy-His and Fleischmann-Veau theories and was adamant about his interpretation. He proposed the theory that the original frontal area was *submerged* by tremendous forward and downward growth of the paired nasomedial processes, implying both *mesodermal infiltration* and *fusion of parts.* He diagramed his merging theory in a chapter on "Normal Development of the Facial Region" for Pruzansky's book *Congenital Anomalies of the Face and Associated Structures.* Then, for *Cleft Lip and Palate* by Grabb, Rosenstein and Bzoch, he discussed the embryology of clefts by comparing three unilateral clefts of the lip: minor, halfway and complete. He noted that the variable in this series



Separate elevations



Separating furrow filling in



Merging complete

is clearly that part of the nasomedial process which contributes to the formation of the median part of the upper lip. . . . On the medial side of the cleft there is a small portion of the prolabium which, by reason of its relation to the midline, could only have been derived from the left

nasomedial process. This process, however, was sufficiently feeble in its growth so that it did not meet and unite with the maxillary process as it normally should. . . . Close scrutiny of the mesenchyme adjacent to the nasal fin of normal embryos reveals that on the nasomedial side the mesenchyme is more richly cellular and more highly vascular. I believe this indicates that it is the prime mover in this important union and that when its growth is inadequate a cleft will remain.

In reference to the accompanying nasal deformity, Patten noted that even when the cleft of the lip is relatively small there is a striking asymmetry in the configuration of the nose. He also noted that

Avery has shown that in cases of unilateral cleft lip there is a marked accompanying deficit in the growth of the nasal capsule on the side of the cleft. This means that the disturbance of the potentialities of the mesenchyme of the nasal processes, which is so obviously involved in defective formation of the fibromuscular part of the lip, is manifested also in its chondrogenic potentialities. It is not surprising, therefore, that the extent of the nasal asymmetry is correlated with the extent of the defect of the lip.

Hamilton, Boyd and Mossman summarized in 1962:

Current embryological opinion regards the elevations or "processes" of the developing facial region as in the nature of surface swellings produced by proliferation of the underlying mesoderm. The furrows between the elevations become smoothed out in subsequent development as growth and fusion of the mesoderm centres proceed beneath the ectoderm.

They cited Streeter's 1948 stand:

Under the circumstances no ectoderm requires absorption; it is simply flattened out in adaptation to the changed surface.

They admitted:

Nevertheless for descriptive purposes, it is convenient to retain the terms maxillary, mandibular and fronto-nasal processes.

Vaclav Karfik

In the mesodermal migration and merging theories when the mesoderm penetration is retarded, the groove persists and disruption along the line of a groove results in a cleft. This all seems simple enough and quite logical. Yet, as Vaclav Karfik

of Prague noted in 1967, it is too simple, for there is no embryonic facial groove to explain the lateral oro-ocular cleft which, although rare, does occur.

OTHER THEORIES

There are other theories besides the failure of fusion, mesodermal penetration or the merging of prominences. There is the theory of failure of the epithelial wall to develop, as proposed by Tondury in 1950, and the rupture of previously formed cysts in the soft tissue bridges, as suggested by Steininger in 1939.

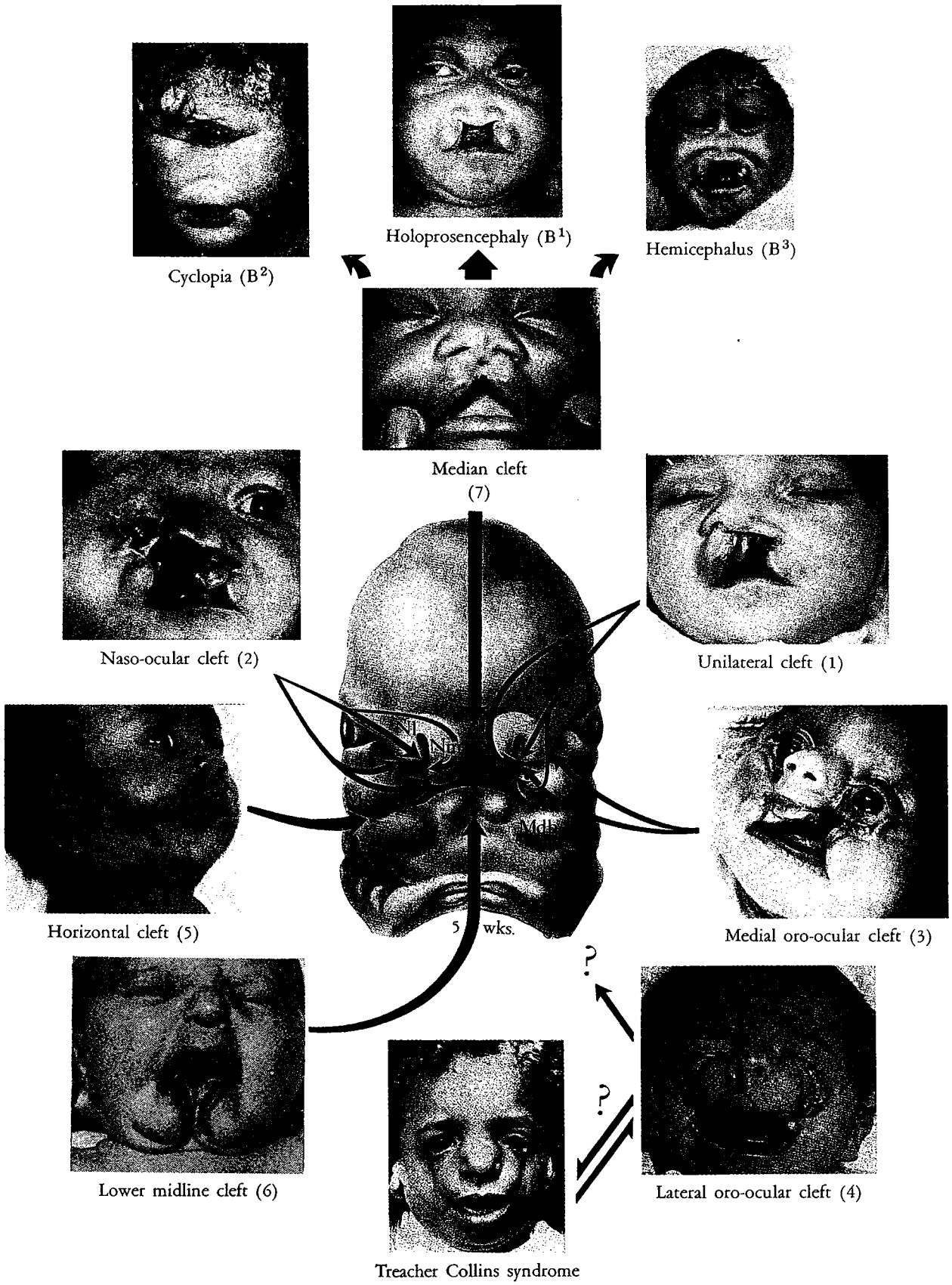
In Hamburg in 1966 Pfeifer offered still another theory. Clefts in which the vermilion ceases at a distance from the nostril with skin and mucosa meeting in the cleft in a scar line flanked on each side by ends of muscle were termed "secondary clefts." Pfeifer proposed the possibility that these were formed not by failure of fusion but by the breakdown of a lip once intact. Here again, to prove the theory we would have to rerun the movie, but preferably backward.

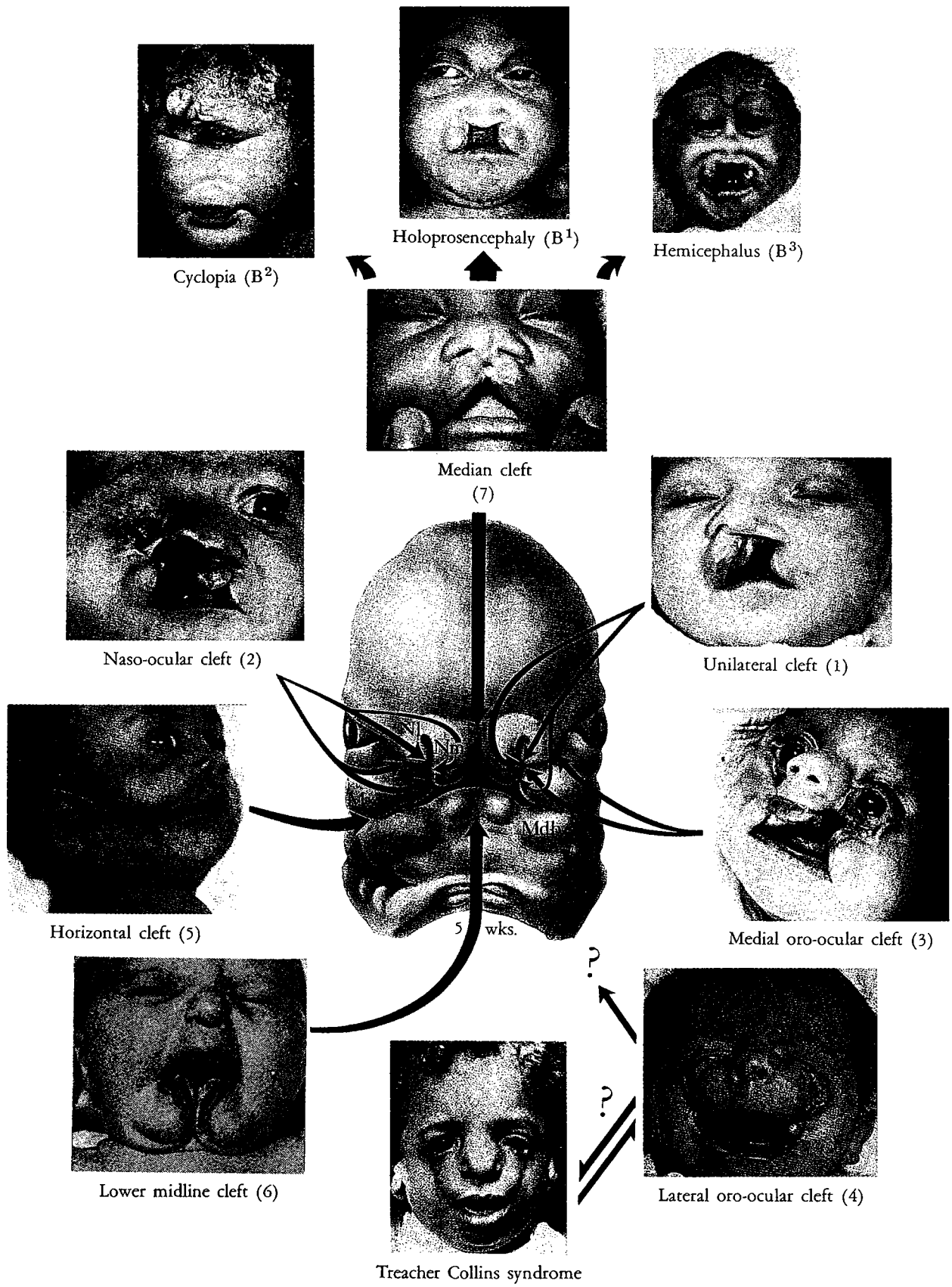
STILL GUESSING

Obviously no theory enjoys universal acceptance, and as no one has been an eyewitness to the entire "in utero show," as yet it is impossible to propose and prove exactly what is happening. Embryologists continue to make educated guesses from 12 single frames, for as of Stark's latest publication only 12 known human embryos with cleft abnormalities had been studied. Of these only one, examined by Tondury, was less than 18 mm., and beyond 18 mm. the facial "clefts" are no longer normally present.

EMBRYOLOGICAL GEOGRAPHY OF FACIAL CLEFTS

With one exception, which is quite rare, congenital facial clefts have been correlated with grooves normally seen in the 6 to 12 mm. embryo. More specifically, a facial cleft has been considered to result from the failure of developing facial prominences


Holoprosencephaly (B^1)
Cyclopia (B^2)
Hemicephalus (B^3)
Median cleft
(7)
Naso-ocular cleft (2)
Unilateral cleft (1)
Horizontal cleft (5)
Medial oro-ocular cleft (3)
5 wks.
?
?
Lower midline cleft (6)
Lateral oro-ocular cleft (4)
Treacher Collins syndrome


Holoprosencephaly (B1)
Cyclopia (B2)
Hemicephalus (B3)
Median cleft
(7)
Naso-ocular cleft (2)
Unilateral cleft (1)
Mn
Mx
Md
5 wks.
Horizontal cleft (5)
Medial oro-ocular cleft (3)
?
?
Lower midline cleft (6)
Lateral oro-ocular cleft (4)
Treacher Collins syndrome

or processes to obliterate these grooves by mesodermal migration or merging. This failure then allows the abnormal persistence of a groove which, in turn, breaks down and produces a cleft. The relationship of facial clefts and embryonic facial geography can be charted in this manner:

"processes" elevations prominences or "hills" are all more or less synonymous

1. *Cleft lip*—failure of both maxillary and nasolateral prominences to merge with the nasomedial prominence. The nasolateral prominence successfully unites with the maxillary.

2. *Oblique cleft, naso-ocular type*—failure of nasomedial, nasolateral and maxillary prominences to merge with each other (example from Bartels, O'Malley, Baker and Douglas).

3. *Oblique cleft, medial oro-ocular type*—failure of maxillary prominence to merge with either nasolateral or nasomedial prominences. There is successful merging of the nasomedial and nasolateral prominences (example is case of Thomas J. Zaydon, Miami).

4. *Oblique cleft, lateral oro-ocular type*—does not correspond to any embryonic facial geography. The cleft traverses the maxilla lateral to the infraorbital foramen (example from Pitanguy and Franco). As noted by L. Hovey, this anomaly bears some resemblance to examples of the Treacher Collins syndrome such as the one published by Rogers in Converse's *Reconstructive Plastic Surgery.*

5. *Horizontal cleft*—failure of maxillary and mandibular prominences to merge (example from Millard and McNeill).

6. *Midline cleft of lower lip and mandible*—failure of merging of the paired mandibular processes (example from Stewart).

7. *Median cleft*—failure of merging of nasomedial prominences. These clefts can be divided into two main groups.

so-called "true" median cleft

A. Failure of mesodermal migration or merging of the nasomedial prominences resulting in a varying degree of a midline cleft (example from Millard and Williams).

So-called "false" median cleft

B. Complete agenesis of the frontonasal process resulting in arhinencephaly, cyclopia, etc.

(1) Agenesis of nasomedial process—nasolateral processes and maxillary processes will merge. In this case there will be absence of the premaxilla, prolabium and nasal columella.

(2) Cyclopia—agenesis of frontonasal prominence including nasomedial and nasolateral processes. Maxillary processes may merge; hence the absence of the nose (example from Millard and Williams).

(3) Hemicephalus with median lip cleft (Darwin's missing link?) (example from W. B. Davis).

This chart only scratches the surface

This classic chart of the geography of facial clefts does give a general surface outline of the position of most clefts but must not be considered the total picture. In 1957, Max Grob of Zurich diagramed the various paths of oblique and transverse facial clefts concluding,

Note inability to explain paths of clefting using classic embryonic concepts.

In 1970 Robert Gorlin of the Division of Oral Pathology, University of Minnesota School of Dentistry, questioned the validity of clefts running along embryologic grooves when he wrote,

Only rarely, however, does the oblique facial cleft follow the epithelial grooves and other explanations should be sought.

Facial grooves are superficial and do not represent actual through-and-through clefts. As pointed out by Otto Kriens, what is more important are the goings-on under the surface as a chain reaction of one fault inducing another. Then to this third dimensional factor must be added also the element of time. It is becoming more and more apparent that clefts occur not over a period of weeks or months but within a very short interval of hours or, at most, days.

Ian Monie

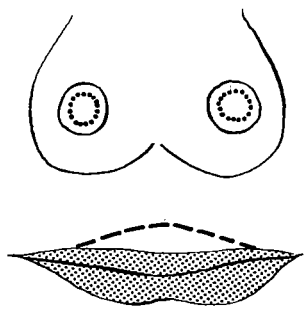
MYSTERY VALLEY

Another area of mystery besides the various cleft formations is the method of creation of the philtrum. Ian W. Monie, a Scottish anatomist from the University of Glasgow, a past president of

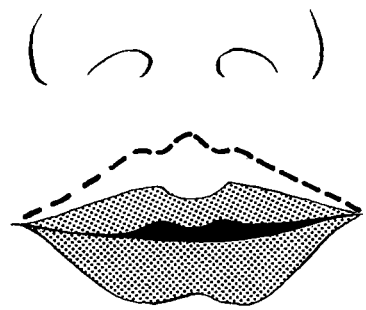
the Teratology Society and a Guggenheim Fellow, has been Professor of Anatomy and Embryology at the University of California, San Francisco, since 1952. In 1972 he wrote:

The study of the philtrum was undertaken because the development of this region seemed to have received relatively little attention. I recall J. B. de C. M. Saunders, Professor Emeritus of Anatomy, drawing attention to this in the course of one of our chats.

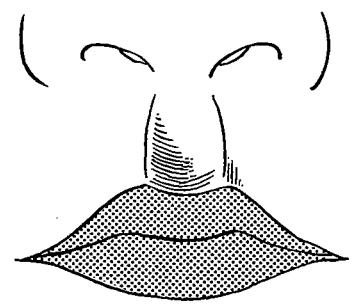
Thus Monie with Cacciatore in their 1962 study of the development of the philtrum noted two previous theories of philtrum formation: (1) persistence of the groove between the globular elements of the frontonasal process (Waterston) and (2) a heaping up of the maxillary mesoderm on either side of the middle line (Boyd). They then proceeded to study transverse sections of the upper lips of embryos, ranging in age from nine weeks to term, along with comparable sections of the upper lip of adult humans. They found no evidence that the philtrum is related to the lines of fusion of facial processes in the embryo. On the contrary, the philtrum does not appear until several weeks after the union of such processes has been completed. They found the philtrum primarily in association with the increasing density of the connective tissue in the median portion of the upper lip and first apparent between the third and fourth months of fetal life. In the September 1962 issue of *Plastic and Reconstructive Surgery,* they diagramed three human embryos to show the timing of the philtrum. At three months (60 mm.) there was a transverse crease but no philtrum, at three and one-half months (85 mm.) a transverse bow-shaped crease but no philtrum and, finally, at four and one-half months (130 mm.) no transverse crease but at last a philtrum.



3 months



3½ months



4½ months

Monie and Cacciatore pointed out that the paramedian eminences which flank the philtrum were found closely associated with the development of the philtrum but were independent of the lines of "fusion" of the facial processes, and although they contain considerable muscle postnatally, their development and configuration seem independent of it.

R. A. Latham, oral biologist at the University of North

Carolina School of Dentistry, stated at the 1973 cleft symposium at Duke, and again wrote personally that

> It is very likely that the philtral dimple is due to an attachment between the lip epidermis and the mid palatal suture; and that the philtral ridges are due to some extent to the flared out posterior ends of the medial crura of the alar cartilages.

He also promised:

> If this is correct, it should be demonstrable and more information will be forthcoming.

In 1973 Latham discarded his previous theory, explaining that

> Studies of the normal fetus show muscle fibers arising from the alveolus in the lateral incisor area coursing anteromedially to insert near the epidermis in the medial philtrum portion of the lip.

As this is contradictory to the findings of Monie and Cacciatore, it may or may not reduce the shadow hovering over "Mystery Valley."

Again, there are missing links, and again, the little embryological data available give us very minimal assistance in surgical correction. Creation of a philtrum still offers difficulty requiring relatively extensive surgical acrobatics.

ACADEMIC INTEREST

The embryological explanation of cleft formation is of great academic interest. No doubt if ever we are able to see an entire trimester movie of cleft formation from beginning to end, we may have better insight into the most appropriate surgical method of correction of the deformity. As today's fantasies are tomorrow's facts, such a movie may not be too far from reality. The fertilized ovum has already been developed and observed in vitro to the one-month stage. Were it not for moral and ethical dicta, space-age scientists could soon solve the mysteries of human development.

Yet, even after complete understanding of how a cleft happens, I am not certain the surgeon's task will be much enlightened. As with any large healed hole which has been created by gunshot, cancer ablation or congenital anomaly, the surgeon, to close it, still must take what he has available to make what he needs.

Anyway, by the time we know *how* a cleft occurs, we probably will know *why* it occurs and can devote less time to its repair and more to its prevention. Unquestionably, cleft causation and prevention is the goal of the future. Yet our knowledge of this subject today is so inadequate that no further lines will be wasted. The subject is now dismissed after the humble acknowledgment that it deserves greatly increased research and many books of its own and that its final solution along with associated findings will be important enough to usher in a new era in the history of man.