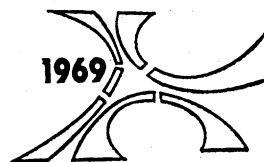


# The Pathogenesis of the Skeletal Deformity Associated with Unilateral Cleft Lip and Palate



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Unilateral conditions of cleft lip and palate consistently show an associated skeletal deformity of which maxillary displacement, premaxillary distortion and malformation of the nose are prominent features. It is thought that the cleft condition, embryologically, represents a relatively minor failure of development and that the skeletal deformity is not part of the original affliction, but rather that it is superimposed upon the facial structure during subsequent development.

While a clear understanding of the pathogenesis of the skeletal deformity is apparently essential in the interests of treatment, present day opinion is divided about its cause and little is known of its mode of development. A detailed histological investigation of the problem was therefore carried out on human specimens of different ages having the unilateral cleft condition. The range of the study was extended by comparison of findings with published descriptions of cleft palate specimens representing other stages of development. As well as inquiring into possible causes, attention was given to the related problems of the time of onset and rate of development of the skeletal deformity.

## Normal Development

In a previous study of the relationship between the cartilaginous nasal capsule and the maxillae in the embryo, a clearly defined ligament was found coursing from the anterior border of the nasal septum to the anterior nasal spine and median suture of the premaxillary region (6). This anterior septopremaxillary ligament appears to be important in the present context for two reasons: firstly, it represents the means whereby the force of the forward growing nasal septum may be transmitted to the developing maxillae, pulling them forwards to insure proper spatial adjustment during rapid growth of the embryonic face;

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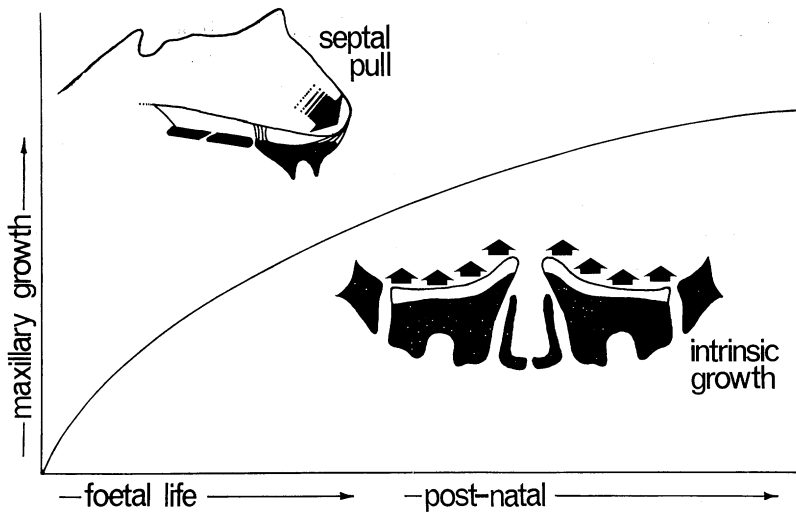


FIGURE 1. Diagram representing the embryonic mechanism (septal pull) and the later fetal mechanism (intrinsic growth) which contribute to normal maxillary growth and displacement.

secondly, for some distance posterior to the anterior septopremaxillary ligament there is no apparent connection between the nasal septum and the premaxillae, a relationship which in the event of a cleft may be regarded as unstable.

Two growth mechanisms, operating consecutively, appear to contribute to prenatal maxillary growth (Figure 1). The first mechanism, already referred to above, commences with the almost simultaneous chondrification of the nasal septum and appearance of the maxillary and the premaxillary ossification centers. The latter centers become connected to the nasal septum by the anterior septopremaxillary ligament and are thereby pulled forwards so that the developing upper jaw shares in the general forward growth of the cartilage making up the embryonic facial skeleton.

The second mechanism becomes active about middle fetal life and appears to be most important soon after birth. This mechanism may be explained in terms of the intrinsic ability of the maxillae for growth upwards and backwards on their free orbital and posterior surfaces (Figure 1). This growth, by occurring against the relatively resistant contents of the orbit and of the pterygopalatine fossa, then displaces the upper jaw downwards and forwards (5).

### Material and Methods

A developmental period from six weeks of prenatal life to about two months of postnatal life was represented by six specimens obtained in Liverpool and by reference to five additional specimens described in

TABLE 1. List of human specimens having unilateral cleft lip and/or cleft palate. Liverpool specimens numbered, others noted by author or source.

<u>AUTHOR</u>	<u>SPECIMEN</u>	<u>AGE</u>
Hoepke-Maurer		6 week
Hochstetter		6 "
Atherton		8½ "
	H201	12 "
	H271	12 "
Veau		18 "
		18 " (twins)
	H893	18 "
	H550	Full term
	H943	Full term
	H948	7 week post-natal
		<hr/>
		Total 11

the literature (Table 1). Parts were removed from the facial skeletons of the Liverpool specimens for histological study as follows: the premaxillary region, the zygomaticomaxillary and pterygomaxillary sutural regions of both cleft and noncleft sides, and the midline portion of the cranial base. In general, these were serially sectioned and representative sections were stained with hematoxylin and eosin and by the Masson trichrome method. Planes of section were chosen to cut sutures transversely—in the case of the deformed premaxillary region the interpremaxillary suture was identified so that it also was cut transversely, that is, in an approximately coronal plane. Control specimens with ages extending over the same period were similarly treated except that younger embryos were serially sectioned in one plane.

### Findings

**SKELETAL DEFORMITY.** Three features of the skeletal deformity in particular appeared to underlie the major part of the deformity as seen clinically: a) lateral displacement of the premaxillary region, b) septal deviation, both horizontally and vertically, and c) upward tilting of the premaxillary alveolar segment.

The premaxillary tilting or rotation was more conspicuous in histological sections and a measure of its extent was evident in the oblique orientation of the interpremaxillary suture (Figure 10).

**DEFORMITY IN THE VERTICAL DIMENSION.** When examined in standard coronal sections through the premaxillary region two distinct phases in the development of the deformity could be identified (Figure 2). A

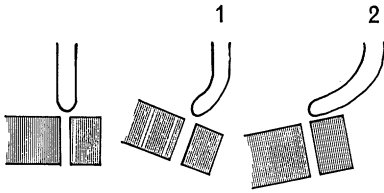


FIGURE 2

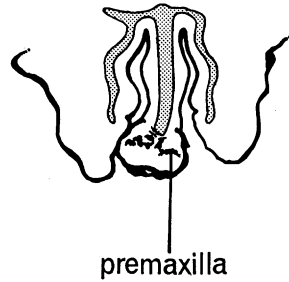


FIGURE 3

FIGURE 2. Diagram illustrating development of vertical deformity. Premaxillary region displaced inferiorly, phase 1; then tilting superiorly, phase 2.

FIGURE 3. Coronal section of Hochstetter embryo, 23 mm C. R., with unilateral complete cleft primary palate, illustrating phase 1 vertical deformity. Redrawn from V. Veau and G. Politzer, Figure 43 (3).

pattern (phase I) of initial deformity was identified in the youngest known embryos having a unilateral complete cleft of the primary palate. The nasal septum showed a deviation towards the noncleft side, the cleft side premaxilla was displaced inferiorly and the interpremaxillary suture was inclined towards the cleft (Figure 3). This pattern was seen again in a young specimen of the Liverpool collection.

It then appeared that at about 12 weeks in fetal life the direction of rotation of the premaxillary region began to reverse. In specimen H.201 (12-week) the interpremaxillary suture overall corresponded approximately to the normal vertical alignment, and complete reversal towards the noncleft side was then observed in all older specimens (Figure 4). The characteristics of the second phase were an interpremaxillary suture with a considerable inclination towards the noncleft side, and an upward tilting premaxillary segment.

Deviation of the nasal septum was a progressive feature throughout, but was so far advanced by 12 weeks as to indicate that it had occurred rapidly prior to that time and progressed more slowly afterwards (Figure 8).

**DEFORMITY IN THE HORIZONTAL PLANE.** Again two phases were recognized in the development of the deformity as seen in the horizontal plane (Figure 5). The first phase corresponded with that described above in the vertical dimension and appeared as a simple deviation of the nasal septum and premaxillary segments towards the noncleft side. Subsequently, and evidently about 12 weeks or earlier, the second phase was entered as the middle part of the septum began to distend towards the cleft side, closely approximating the nasal conchae.

An embryo of eight and a half weeks, demonstrating the considerable degree of septopremaxillary deviation which had occurred in the first phase of development, has been described by Atherton (1); and an ex-

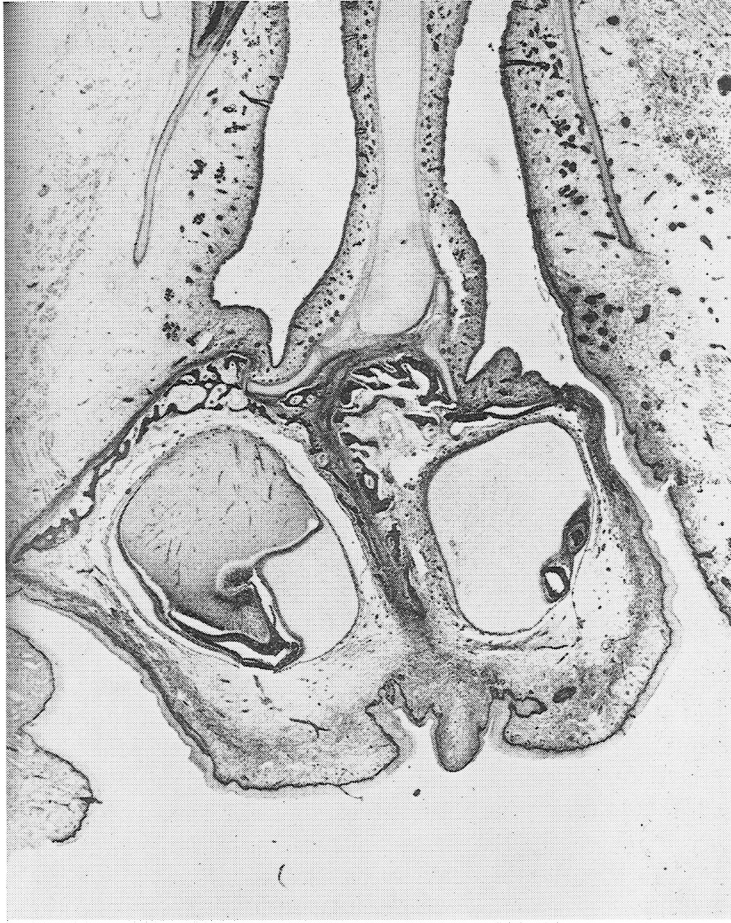


FIGURE 4. Coronal section of premaxillary region of H893 (18 wk.) with unilateral incomplete cleft primary palate, illustrating phase 2 vertical deformity. Inter-premaxillary suture inclines to noncleft side (compare Figure 3).

ample of the second phase of the horizontal deformity has been illustrated by Veau (3) in an 18 week fetus (Figure 6). In Veau's specimen, the cartilaginous nasal septum and the vomer are arched against the nasal wall of the cleft side, compressing the conchae, while the nasal cavity on the noncleft side is widened.

Another feature associated with the septal distension was that the vertical alignment of the nasal septum and the interpremaxillary suture was disrupted. Anteriorly the septum remained in close relation to the suture, the two being held together by the septopremaxillary ligament, but posteriorly they separated, the middle part of the septum having distended towards the cleft side and the suture having been displaced towards the noncleft side (Figures 5 and 7).

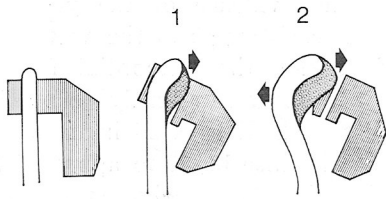


FIGURE 5



FIGURE 6

FIGURE 5. Diagram illustrating development of horizontal deformity. Initial deviation of septopremaxillary region to nonleft side, phase 1; subsequent superimposition of septal distension and dislocation, phase 2.

FIGURE 6. Horizontal section of Veau fetus, 165 mm C. R., with unilateral complete cleft lip and palate, illustrating phase 2.



FIGURE 7. Coronal section H948 taken from middle premaxillary region showing dislocation of nasal septum (S) and interpremaxillary suture (I) occurring in phase 2.

### Discussion

**ONSET AND RATE OF DEVELOPMENT.** The evidence of the youngest known human embryos with a unilateral cleft supports the view that at the crucial time of initial cleft formation the primordial face is symmetrical (at 33–35 days) and that deformities, evidently caused by a condition of unbalanced development, arise in the period immediately following when the skeletal structures of the face begin to appear. The 41-day embryos of Hochstetter and Hoepke-Maurer showed a small degree of deviation of the nasal septum and premaxillary region consistent with the belief that the skeletal deformity was at a very early stage of formation as opposed to its emergence as a miniature of the deformity seen at birth. Since skeletal deformity was readily seen in these embryos of six weeks, it may be said that deformity had commenced earlier in the sixth week, that is, very soon after initial cleft formation (Figure 8).

The 12-week specimen (H. 201) showed a relatively severe deformity despite the fact that the primary palatal cleft was not complete, and it may be inferred that if the cleft had been complete the severity of malformation of the facial skeleton would have been greater in this specimen. This expectation is borne out in a specimen (X2336) illustrated by Kraus, Kitamura and Latham (4). Clearly, the skeletal deformity is well established by 12 weeks of fetal life, although not exhibiting all of the characteristics present at birth. If the degree of septal deviation were to be used as a measure of the increasing skeletal deformity, it is suggested that the resulting curve might be similar to that illustrated in Figure 8. It appears that the skeletal deformity develops rapidly in the embryonic and early fetal periods and that its severity slowly increases towards full term.

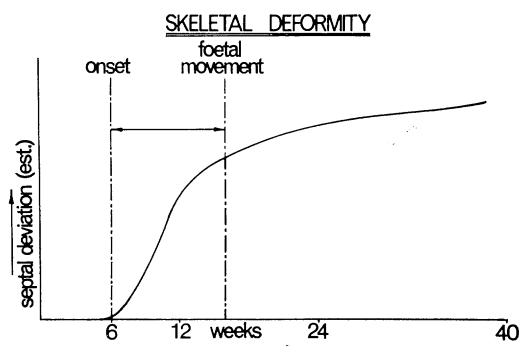


FIGURE 8. A scheme relating the estimated degree of septal deviation to a time scale to show early appearance of skeletal deformity before development of functional factors, e.g. muscle contraction.

## MECHANISM OF SKELETAL MALFORMATION

*Phase I.* In the period following initial cleft formation, gross morphological changes normally occur in the embryonic facial region due to the rapidly developing skeletal structures (nasal capsule and Meckel's cartilage). It is much more probable that the growth of these supporting tissues are responsible for the secondary complications around the original cleft than the developing musculature (2) which is not functional until later in fetal life (Figure 8). The hypothesis that the cartilaginous nasal septum plays a leading role in the production of the secondary facial deformities may now be examined.

The septum has a downward and forward direction of growth. In the event of a unilateral cleft the normal resistance to septal growth would be lacking on the cleft side. The septum and attached premaxillary region would be expected to swing downwards, forwards and to the noncleft side and the interpremaxillary suture would then be inclined towards the cleft. This is precisely what has happened in the six-week embryos of Hochstetter and Hoepke-Maurer (Figure 3). It is probably more correct to say that unilateral restraint from the normal side via the septopremaxillary ligament pulls the growing nasal septum off course, so that both septum and maxilla swing inferolaterally due to the dominant growth of the nasal septum at this time (Figure 9).

*Phase II.* To understand the second phase of the deformity (the reversal of the premaxillary rotation), we have to ask, "What will be the effect of a severely bent septum whose growth direction has changed?" If the nasal septum is regarded as being of essentially normal proportions, the fact that it is bent means that its vertical height is reduced. A bent septum must mean deficiency of premaxillary height and interference with the normal descent of the upper jaw with growth. When the maxillae then develop their own intrinsic growth force which continues downward and forward displacement, descent of the noncleft maxilla will be hindered medially by attachment to the bent septum. The noncleft maxilla in growing downwards therefore rotates medially and the obliquity of the interpremaxillary suture becomes reversed (Figure 10). Reversal of the orientation of the interpremaxillary suture may be attributed mainly to interference with the normal downward and forward displacement of the maxilla by the deformed septum. While the actual displacing force at this time appears to come from the maxilla itself as growth activates on the free orbital and posterior surfaces, it is also possible that some initial displacement is due to downward expansion of the growing eyeball.

The distension of the middle part of the nasal septum described as phase II of the horizontal deformity was the apparent cause of the narrowing of the nasal cavity on the cleft side, and of the dislocation of



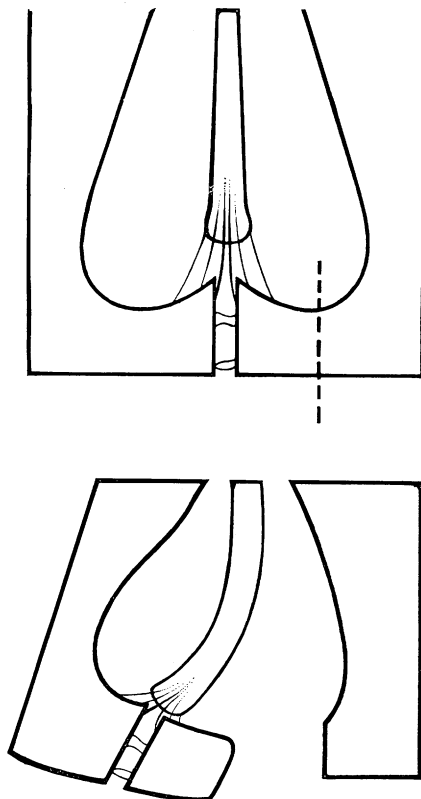


FIGURE 9. Diagrams illustrating mechanism of phase 1 (vertical deformity). Top, normal relationship between nasal septum and upper jaw showing symmetrical septo-premaxillary ligament. Bottom, unilateral restraint of nonleft side pulls growing septum off course.

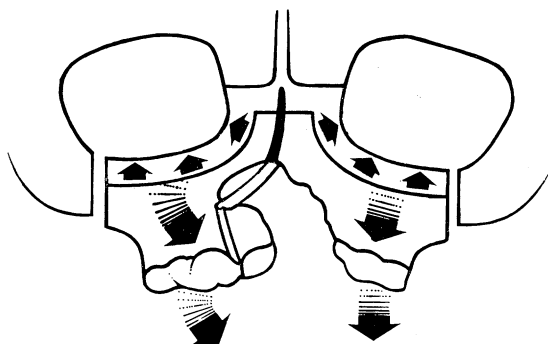


FIGURE 10. Diagram illustrating the production of phase 2 of vertical deformity by interference with downward displacement of upper jaw as maxillary growth on orbital and posterior free surfaces provides the motive force. Nonleft maxilla rotates medially, tilting premaxillary region upwards.

the inferior septal border from the interpremaxillary suture. This is readily understood in terms of normal structural relationships in early fetal life when the anterior septopremaxillary ligament was the principal means of attachment between the nasal septum and the upper jaw. Following an initial deviation of the nasal septum, the site of application of septal pull would be no longer in alignment with the remaining midline portion of the septum, continued growth of this pliable structure would tend to make it bend further, merely resulting in its distension into the nasal cavity of the cleft side instead of delivering its growth force forwards to the premaxillary region (Figure 5).

### Conclusions

a) The primacy of nasal septal growth in the embryonic period appeared to be the major cause of the skeletal deformity. b) The anterior septopremaxillary ligament dictated the nature of the septal deviation. c) The skeletal deformity had its onset during the sixth week of embryonic life, developed rapidly until about 12 weeks after which its progress became slower. d) The deformity developed in two distinct phases which appeared to be governed mainly by two facial growth mechanisms acting consecutively. e) An initial rotation of the premaxillary region was reversed at about 12 weeks to give the upward premaxillary tilt and obliquity of the interpremaxillary suture typically seen at birth. f) Malalignment of the nasal septum and interpremaxillary suture in the middle premaxillary region was attributed to the lateral septal distension occurring in the second phase and to the lack of septopremaxillary attachment.

### Summary

The cause and mode of development of the skeletal deformity associated with unilateral cleft lip and palate were investigated histologically using six human specimens and by comparison of these with specimens illustrated in the literature. Deformity first appeared in the sixth week and increased rapidly in severity until about 12 weeks, thereafter progressing more slowly. The deformity developed in two phases. The initial deformity corresponded to expectation assuming the validity of the nasal septal concept of growth. The final deformity was characterized by an upward tilting premaxillary region which appeared to result from interference by the bent nasal septum with subsequent downward displacement of the maxillae by an intrinsic growth mechanism. The primacy of nasal septal growth in the embryonic period appeared to be the root-cause of the deformity. Distension of the middle part of the nasal septum and retarded downward displacement of the premaxillary region were secondary complications. A key factor

in determining the actual form of the skeletal deformity was the presence of the anterior septopremaxillary ligament.

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