Cleft Palate and Associated Anomalies in A 30 mm C.R. Length Human Embryo

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The pathogenesis of cleft palate has been the subject of several investigations (1, 10, 11, 13, 16, 17, 19, 21). Nevertheless there is still controversy whether the defect is the result of a failure of fusion of the palatal folds as suggested by Arey (*2*), Hamilton, Boyd & Mossman (*5*), Latham (*12*) and Subtelny (*20*), or because of a post-fusion rupture as postulated by Kitamura (*10*), Kraus (*11*) and Lejour (*13*). According to Kraus (*11*) the latter mechanism is said to account for the formation of cleft palate in man. However, in the course of our studies on the development of the nerve supply to the human tongue, we encountered a 30 mm C.R. length human embryo which showed features strongly suggestive of a pre-fusion type of cleft palate. A search through the literature revealed that cases of arrested development at this crucial stage are rarely documented and it was therefore felt that a short report on this embryo might help to reassert the contention that cleft palate in man also may result from a failure of fusion of the palatal folds. Further, our findings suggest that the vital underlying mechanism causing this anomaly may reside in one of the primary embryonic layers.

Materials and Methods

Complete serial sections of 15 human embryos ranging from 17.5 mm to 37 mm C.R. length and belonging to the late Professor J. D. Boyd's collection at the Anatomy School, Cambridge, England were examined during the current investigation. All specimens were cut in the coronal plane; other details are shown in table I.

Results

In the normal series of human embryos ranging from 17.5 to 37 mm C.R. length, the progressive changes in the development of the primary palate and the fusion of the palatal folds were observed. The primary palate was in evidence in the 17.5 mm embryo, while only the rudiments

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TABLE 1. Details of embryos studied.

No.	*C.R. length (mm)*	*thickness of sections (μ)*	*No. of embryos studied*	*stains used*	*fixation*
1	17.5	10	1	DeCastro	DeCastro
2	20	7 & 10	3	Bodian, H & E, P.A.S.	Formalin-Bouin
3	21	7	1	Bodian, H & E, Trichrome	Formalin-Bouin
4	23	10	1	Bodian, Gomori-Hexamine	Formalin
5	28	6 & 10	2	Bodian, H & E	Formalin
6	30	10 & 12	3*	DeCastro, H & E	DeCastro
7	33	7	1	H & E, Trichrome	Zenker Formalin
8	35	15	2	Bodian, DeCastro	DeCastro
9	37	7 & 10	1	H & E, Trichrome	Bouin

* one abnormal

of the palatal folds were present in both the 17.5 and 20 mm embryos. In the 21 mm embryo the palatal folds were much larger and by the 23 mm stage (Figure 1) they were seen to hang loosely on either side of the tongue. By the 28 mm stage (Figure 2) the folds had lifted clear of the tongue, assumed a more horizontal position and were separated only by a very narrow interval. In the 33 mm embryo the folds had fused and were separated only slightly in the posterior one-third. In the 35 mm embryo this fusion had progressed posteriorly reaching almost the terminal end of the soft palate, while fusion was complete in the 37 mm embryo.

In the abnormal 30 mm embryo the area of the primary palate was formed in the usual manner but the epithelial surfaces of the dorsum of the tongue and the septum of the nose were apposed while the buccnasal chamber was clearly seen only on the right side. The nasal septum was deviated to the left and this almost obliterated the left nasal cavity. The two palatal folds hung like curtains on either side of the tongue and the surfaces were also apposed to those of the tongue. Selected coronal sections depicting the position of the palatal folds in relation to adjoining structures are shown in Figures 3–6. The relationship of the palatal folds to the tongue in the abnormal 30 mm embryo appeared to correspond closely to the 23 mm stage of normal development. The tubo-tympanic cavities of both the right and left sides were very small and their walls were still apposed in many places. The anterior portions of the nasal cavities were completely occluded by epithelial cells whereas this feature was much less extensive in the normal 28 mm and 33 mm embryos.

There were other associated abnormalities. In the *thorax* adhesions of both the right and left lungs to the lateral body wall were seen and these were pronounced on the right side. Part of the right ventricular wall was

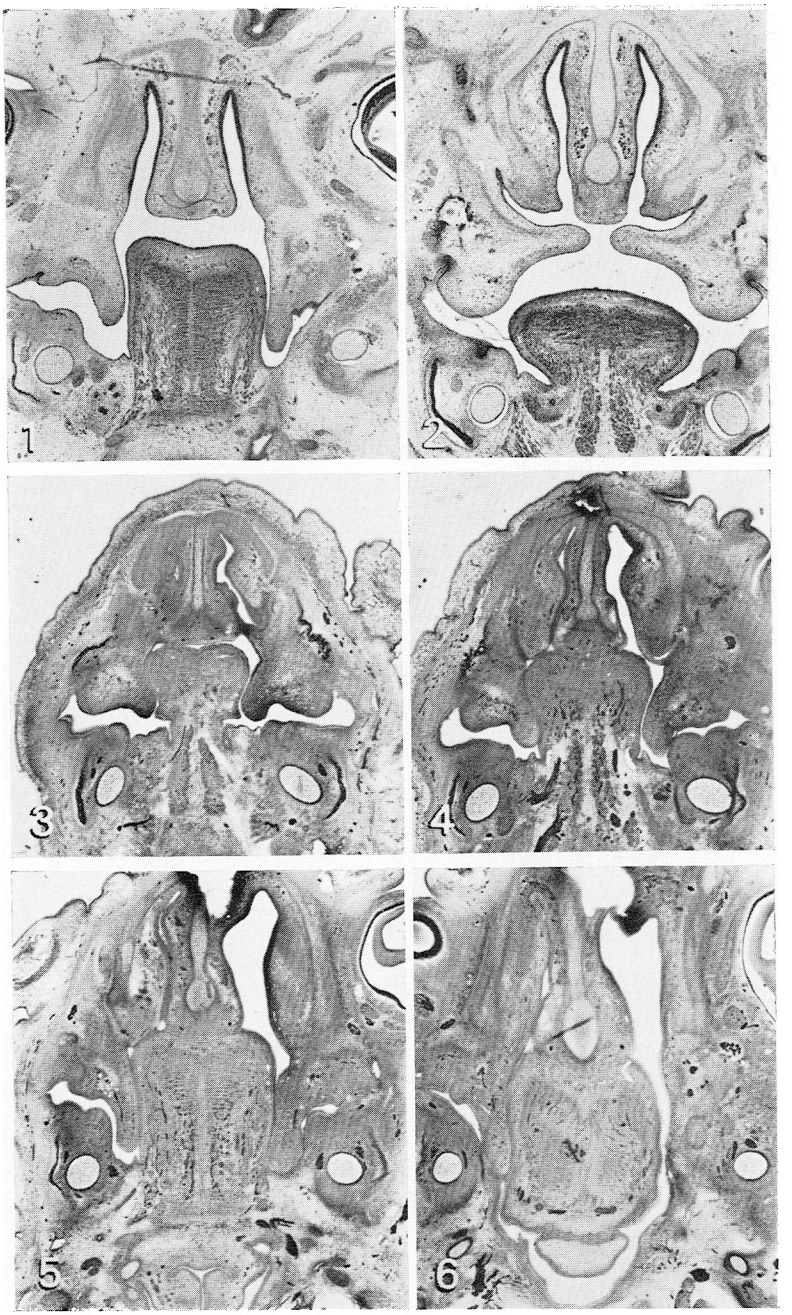

FIGURE 1: Coronal section of a normal 23mm C.R. length human embryo showing palatal folds hanging vertically on either of tongue.

FIGURE 2: Coronal section of a normal 28mm C.R. length human embryo showing palatal folds in the horizontal position.

FIGURES 3–6. Abnormal 30mm C.R. length human embryo. Selected coronal sections sequentially arranged anterioposteriorly showing vertically placed palatal folds and the apposed epithelial surfaces.

adherent to the anterior thoracic wall as well as to the diaphragm. In the *abdomen* adhesions between mid-gut and the liver were observed. The lesser sac cavity was reduced, being partially obliterated and there was continued adhesion of the right suprarenal to the liver and the liver to the body wall, so that there was very little extension of the greater sac of the peritoneum onto the right side. In the *brain* the left cerebral hemisphere was small whereas the right hemisphere was relatively larger. The right hemisphere showed an ingrowth from the anterior wall, which in sections appeared as a ring of nervous tissue inside the ventricular cavity.

Discussion

It is of interest to note that Kitamura (*10*) and Krause (*11*) have questioned the assumption that the mechanism of cleft palate formation is the same for both man and non-primate experimental animals. They believe that clefts in man are mainly of the post-fusion type. While such a possibility cannot be denied, our findings in the 30 mm human embryo clearly indicate that there could also be a failure of fusion of the palatal folds leading to pre-fusion clefts similar to those reported in non-primate animals. Consequently, our present observations support the concept of Latham (*12*) that palatal cleft in embryos may result from a failure of elevation and subsequent fusion of the palatal folds. Therefore, it is likely that both types of cleft palates could occur in man, depending on the stage at which there is a pathological assault on the embryo. Thus, involvement in the early stages of development could lead to an arrested growth resulting in a pre-fusion cleft whereas later interferences could give rise to post-fusion clefts.

Although congenital malformations are known to occur in human embryos, a complete series showing the pathogenesis of a specific defect is not readily available. Therefore a great deal of information has been acquired from animal studies (3, 6, 7, 14, 15, 18). Moreover, animal studies have revealed that congenital malformations could be artificially induced by an alteration in the environment of the embryo. A comprehensive review on the subject is given by Warkany & Kalter (*23*). However, none of these studies have attributed these malformations as being primarily due to some failure of mechanisms residing in one or the other of the primary germ layers—ectoderm, endoderm or mesoderm. The abnormalities in the present case seem to suggest an aberrant development within the mesoderm. It may well be that the dissolution, movement or even growth of the mesodermal tissues is defective or uncoordinated, producing distorted dimensions of the natural body cavities, which in turn will result in apposed epithelial surfaces of the oral, nasal, pleural and peritoneal cavities (*8*) and the tubo-tympanic recesses (*9*) as seen in the present case. Indeed, the concept of a lack of coordinated movement of mesodermal tissue is in accord with the recent findings of Walker (*22*)

that the rotation of the palatal folds is related to an increased synthesis of sulphated mucopolysaccharides within the mesenchymal ground substance of the palatal folds. Perhaps the failure of the palatal folds to assume a horizontal position in the present case could be due to defective synthesis of these sulphated mucopolysaccharides. Such a failure might result in the palatal folds becoming apposed to the sides of the developing tongue as seen in the abnormal 30 mm embryo.

Finally, the anomalies observed in the cerebral hemisphere, where there was an overdevelopment of one and a defective formation of the other, could be due to an imbalance in the influence of the mesoderm controlling the growth of the brain. In this connection, transplantation experiments by Ebert (*4*) have shown that mesoderm does indeed control the development of the nervous system.

Summary

A case of cleft palate and associated anomalies occurring in a 30 mm C.R. length human embryo is presented. It is suggested that the cleft palate in this embryo is due to a lack of elevation and subsequent fusion of the palatal folds caused by an abnormality within the mesoderm.

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