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The normal and abnormal development of the central facial areas

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The embryonic face bears no resemblance to the human face at birth. Two portions characterize the head of the human embryo: a dorsal one, which contains the brain, a ventral one, which includes the primitive oral cavity (stomodaeum) with its appendages and which contributes to the formation of the face. The entry of the stomodaeum is delimited in the upper part by the frontal eminence, below and at the sides by the mandibular arch in which a superior (maxillary) and an inferior (mandibular) process are distinguishable. At this stage, – end of the fourth week –, two olfactory placodes of elliptical shape appear on either side of the frontal eminence. They form the depressions which will develop into the olfactory pits.

With the appearance of the two olfactory pits the development of the face begins. It becomes modelled by means of fixed furrows which appear at constant places (Figure 1). A sagittal and paramedially running furrow begins in the region of the future upper lip and terminates foreheadwards with

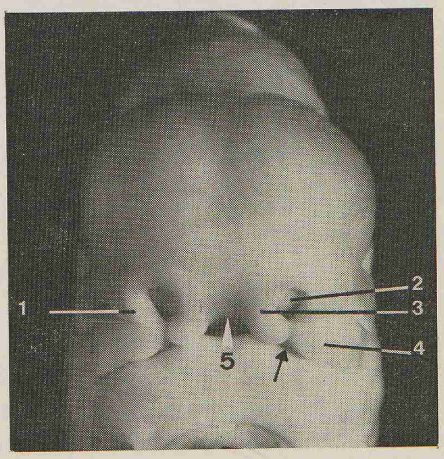

Figure 1. Head of a 10 mm embryo seen from the ventral side. 1. lateral nasal process, 2. olfactory pit, 3. medial nasal process, 4. maxillary process, 5. incisura interglobularis. Arrow points to the primary palatine groove.

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a widening which corresponds to the external nares. One speaks about the primary palatine groove from which springs the nasolacrimal groove which runs diagonally ascending toward the eye. These furrows separate fixed, clearly raised areas, which are designated as facial processes. Medially from the primary palatine furrow is situated the medial nasal process, and laterally the lateral nasal process. These "processes" are brought out in relief from one another, however, only in the range of the furrow, passing over peripherally without limite to the neighbouring area.

One has regarded these "facial processes" as independent formations and the furrows separating them as genuine clefts. In the shaping of the final face they are said to grow together and fuse with one another. Examination of well-fixed embryos convinced us that *any fissure revealed in the embryonic face must be considered to be a pathologic finding*. The characteristic aspect of the embryonic face with its grooves and bulges depends on the uneven distribution of the subepidermal mesenchyme. *The transformation of the embryonic face is not effected by a secondary fusion of processes which up to that time had been separate and distinct, but by a gradual filling or levelling up of the grooves which disappear with the thickening of the mesenchymal layer beneath the epithelium.* The swellings which appear in embryos of 4-6 mm have already disappeared in embryos of 18 mm.

The median frontal eminence is modelled by the brain which shows in this early stage two sections, the caudal rhombencephalon and the rostral prosencephalon. The prosencephalon (forebrain) grows rapidly in a foreward and downward direction and subdivides into the telencephalon and the diencephalon. It forms the foremost part of the embryonic head and models the prominent frontal eminence. The development of the middle area of the face is therefore closely linked with the development of the forebrain. Disturbances of its development will result in deformation and, in the most severe cases, in agenesia or hypoplasia of the frontal eminence, as occurs in pronounced form in cyclopia and arhinencephalia, where the entire central region of the face is absent or deformed.

The maxillary and mandibular processes provide the structures of the lateral and lower facial regions. These processes consist of actively proliferating mesenchyme stemming partly from the mesoblast and partly from the neural crest.

The elliptical nasal placodes appear as convex thickenings of the surface ectoderm. Growth changes of the forebrain and the proliferation of the surrounding mesenchyme accompanying the formation of the medial and lateral nasal folds cause the sinking in of the nasal placodes to the olfactory pits (Figure 1). The openings of these pits soon become to lie at the margin of the oral cavity where they are bounded by the medial and lateral folds.

With the transmutation of the nasal placodes into olfactory pits the frontal eminence is subdivided into an upper and a lower part, which are separated by the sulcus supranasalis. The upper part of the frontal eminence, the rudimentary forehead, continues to be modelled by the growing telencephalon. The lower part provides the external nose and the prolabium (Figure 1). It is divided by the wide nostrils into one broad median and two narrow lateral areas. The median area comprises the two medial nasal processes, which surround the nasal pits medially and terminate in the processus globulares, and a central zone connecting the two medial nasal processes which does not extend as far downwards as the processus globulares. Its lower edge appears as an incision between the two processes, – the *incisura interglobularis*. The two lateral nasal processes delimit the olfactory pits laterally and come into contact with the maxillary process in the nasolacrimal furrow. *How do the enclosed nasal cavities develop from the wide open olfactory pits?* The lateral nasal processes increase rapidly in height, grow, – as frontal sections show –, downwards and connect with the medial processes. This is the beginning of a process of epithelial coalescence which, progressing from back to front, closes the olfactory pits in the manner of a zip-fastener up to the small outer nasal openings (Figure 2).

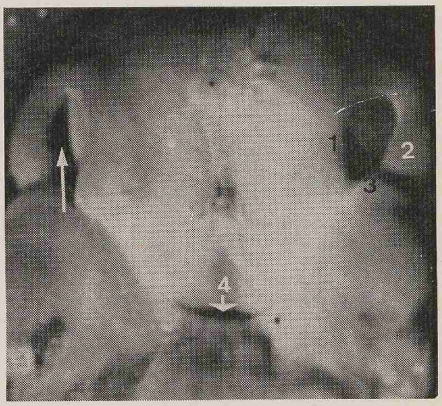

Figure 2. Vault of the primary oral cavity in a 7,5 mm embryo. 1. lateral, 2. medial nasal process, 3. maxillary process, 4. Rathke's pouch. Arrow in the right olfactory pit shows the direction of the coalescence of the nasal processes.

In frontal sections, one finds at the point of the fusion of the two nasal processes an epithelial wall (nasal fin), which extends from the floor of the nasal cavity to the roof of the oral cavity and develops as a result of apposition and fusion of the epithelial investments of the two nasal processes (Figure 3). Externally its position is revealed by the fine primary palatine groove. In the anterior area the epithelial wall is supplemented by the coalescence of the maxillary process with the medial nasal process, i.e. the floor of the nasal cavity is closed by coalescence of the two nasal processes. The

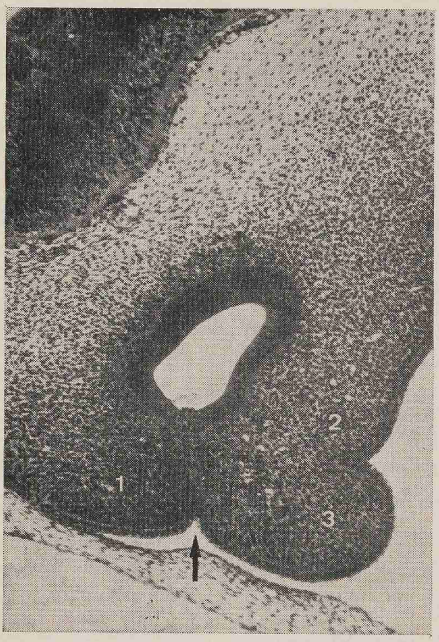

Figure 3. Frontal section of the primitive nasal cavity of an embryo of 9 mm. - 1. medial, 2. lateral nasal process, 3. maxillary process, arrow indicates the primary palatine groove and the epithelial wall.

suture between the maxillary and the medial nasal processes unites on both sides the lateral third and the middle third of the upper lip.

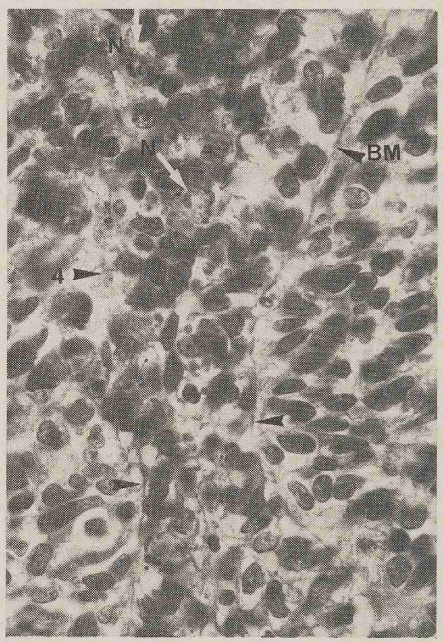

Figure 4. Frontal section of the epithelial wall. BM basal membrane partly dissolved (4), arrows indicate necrotic cells.

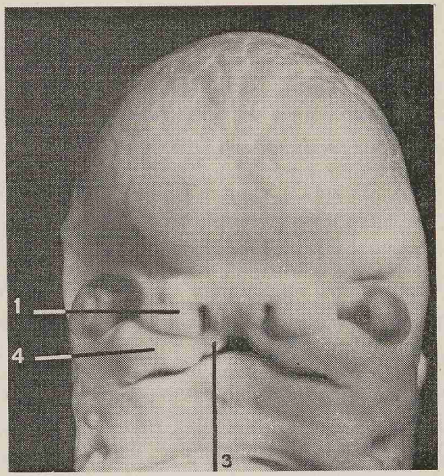

Figure 5. Head of an embryo of 18 mm. The fusion between the lateral (1) and medial (3) nasal processes and the maxillary process (4) is completed. Notice the sulcus supranasalis, the hypertelorismus and the flat, broad nose. The incisura interglobularis is still visible.

Subsequently the epithelial wall is rapidly dissolved and replaced by mesenchyme. This mesenchymal consolidation begins in front and spreads first to the middle area of the wall: here cell necrosis occurs, the basal membrane is dissolved and invasion by mesenchymal cells and makrophages takes place (Figure 4). Thus we have the development of a mesenchymal plate, – the *primary palate* –, which separates the primitive nasal from the oral cavity. The occipital part of the epithelial wall is preserved longer, cell pyknoses do not occur, the wall is forced apart and becomes the bilaminated membrana bucconasalis, which finally ruptures and opens the primitive choana. This is the case in embryos of about 18-20 mm. These embryos have a broad, flat nose with slit-shaped nostrils (Figure 5). The two halves of the nose have come closer, the incisura interglobularis is still clearly visible and pronounced hypertelorismus exists. It is only with the development of the cartilaginous-bony skeleton that the nose achieves its final form. The face becomes narrower and the eyes, having moved closer together now look in a forward direction.

On the development of various major malformations of the central facial areas.

We must differentiate in terms of the timing of their development between two groups of congenital malformations of the central facial areas:

1. Malformations which are attributable to a defective development of the forebrain and determined in a very early phase, and
2. congenital deformations originating in a later phase and confined exclusively to the central facial region, leaving the forebrain and the eyes unaffected.

Re 1: The malformations of the first group include the cyclocephaliae and the arhinencephaliae, in which the central facial area is absent or severely deformed. The head of a full term cyclops, with its single eye surmounted by the proboscis, hardly seems to be human at all, whereas the arhinencephalic new-born, despite the malformed nose, the median cleft lip and the extreme hypotelorism, is still reminiscent to some extent of the face of a normal new-born infant. Morphologically, they do not differ fundamentally; on the contrary, arhinencephaly represents merely a less severe degree of the same disturbance as found in cases of cyclopia. These are fundamental malformations which can also be produced experimentally in amphibian and chicken embryos and are attributable to a failure of the cephalic organizer.

Re 2: Among the malformations of the second group we include cases of fronto-nasal dysraphia, nasal duplication, nasal aplasia, choanal atresia and nasal deformities combined with lateral facial clefts.

a. *Frontonasal dysraphia.* – These comprise all congenital defects in the area of the median line of the face. We are familiar with an uninterrupted series ranging from extremely severe forms to simple median fistulae and cysts in the area of the bridge of the nose.

1. *Median clefts of the upper lip.* – In the least severe cases the malformation is limited to a median groove or to a small free-cornered defect in the centre of the upper lip. The defect can reach the alveolar process and may possibly be combined with a median maxillary cleft. More severe forms also exist, in which the defects are associated with agenesia of the entire inter-maxillary segment. Children suffering from this kind of defect always have a brain deformity in the sense of a holoprosencephalia with absent bulbi and tractus olfactorii and are to be classified as arhinencephalics. The aplasia of the inter-maxillary segment is therefore a pathognomonic symptom of the existence of a deformity of the forebrain.

2. *Median nasal clefts.* – In this deformity the septum nasi is split into two divergent halves. The cleft, covered by the skin and of variable width, is located on the broad bridge of the nose. In the case of total cleavage, the nose consists of two entirely separate halves, – 'bifid nose' –, each half having its own medial wall. The malformation is associated with a broad nasal root and pronounced hypertelorism, and possibly with other defects such as a broad median cleft of the upper lip, absent inter-maxillary area, cleft palate and choanal atresia. Both halves of the nose may be symmetrical, but one half is frequently under-developed. The median cleft is usually broader at the bottom than at the top. In such cases hypertelorism may be absent.

Most of the cases of median nasal cleavage described in the relevant literature

are sporadic observations. In a few cases autosomal, dominant inheritance and familial occurrance have been described.

How do median clefts of the upper lip and nose develop? – They are manifestations of one and the same disturbance and have a common pattern of development. In the simplest case, – isolated median cleft of the upper lip –, the incisura interglobularis is preserved. In pronounced cases, the coalescence of the two medial, relatively widely spaced nasal processes has not occured due to the fact that the central section of the frontal eminence has not – or not properly – filled up with mesenchyme. The result of the disturbance is dependent on the state of development of the nose when the noxa begins to exercise its effect.

b. *Nasal duplication.* – It is important to differentiate between cases of a complete median nasal cleft, with each half of the nose having only one nostril, and cases of true nasal duplications which, in their most pronounced form, have two nostrils on either side.

Cases of true nasal duplication belong to the *diprosopiae* (facial duplication). They have a single occiput and a duplicated face with four eyes, two noses and two mouths. Among these, children have been observed with median synophthalmus or with three and two eyes, respectively. The unifaction of the two mouths leads via an intermediate stage to macrostomia; unifaction of the two noses begins with the coalescence of the two medial wings of the nose. The bridge of the nose remains duplicated and shows a central depression, consistent with the double septum. The intermediate nostril can ultimately disappear, so that only the tip and the bridge of the nose are duplicated.

Cases of facial duplication are nothing else but a minor manifestation of a duplicitas anterior. Isolated nasal duplication (rhinodymia) in otherwise totally normal conditions must be regarded as localized facial duplication.

c. *Nasal aplasia.* – Cases of bilateral aplasia are extremely rare, unilateral aplasia may occur in children who are otherwise quite normal. On the defective side the nasal skeleton and the ductus lacrimalis are absent. The missing half of the nose may be replaced by a proboscis lateralis. Unilateral underdevelopment of the nose may be associated with various other defects such as labial cleavage and microphthalmus.

d. *Choanal atresia.* – Unilateral cases are more common than bilateral and girls are more frequently affected than boys. The atresia may be either membranous or osseous. It may be a question here of the persistence of the membrana bucconasalis, which closes the primitive choanae in the embryo. In normal circumstances the membrane is a double epithelial diaphragm which perforates rapidly. If, abnormally, fibroblasts succeed in penetrating the membrane, the membrane will be preserved.

Choanal atresia is not infrequently associated with other defects such as facial asymmetry, cleft palate and eyelid coloboma. Occasionally it is also accompanied by atresia of the external auditory meatus.

e. *Nasal deformities associated with lateral facial clefts.* In contrast to the median facial clefts which develop as the result of the failure of the zona internasalis to fill up with mesenchyme, lateral clefts of the upper lip are true clefts which develop due to the absence of the epithelial wall between the two nasal processes on the one hand, and the medial nasal process and the maxillary process on the other. The exact genesis of lateral clefts is still subject to discussion, but it seems in many cases that it is the resulting condition of a hypoplasia of one of the processes involved in the suture. This is for example indicated by findings in a human embryo of 13 mm, which showed cleavage on the left side in a typical position (Figure 6): On the right side the nasal cavity was closed with the exception of the external slit-shaped nostril. On the left it took the form of a deep groove which opened broadly into the primitive oral cavity. Compared with the right side, the lateral nasal process and the maxillary process showed marked retardation of growth and were not in contact at any point with the medial process. In another embryo measuring 12 mm we found a different situation (Figure 7): The epithelial wall had developed normally, but contained on both sides at the time of the interruption of pregnancy countless necrotic cells in dissolution. The anterior area of the wall was completely disorganized and in total disintegration.

Both these observations indicate that, having regard to their development, at least two different forms of fissure can be expected. In the first case it was the question of a primary cleft, which developed as a result of the fact that epithelial coalescence of the two nasal processes did not occur. In the second case the epithelial wall had formed but was in complete dissolution at the moment of examination. There were no signs of mesenchymal consolidation. If the embryo had continued to develop, a bilateral secondary cleft would very probably have formed.

Experiments in rats, for which we used hadazidine, an antibiotic isolated

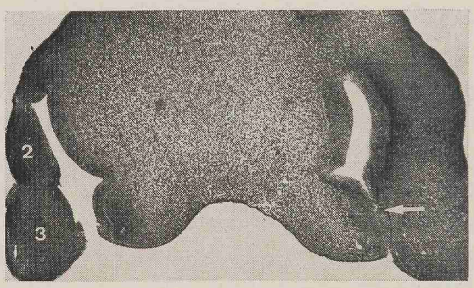

Figure 6. Frontal section of the nasal region of a 13 mm embryo, carrier of a left embryonal fissure. Notice the total absence of the epitheial wall and the retarded growth of the left lateral nasal (2) and maxillary (3) processes. Arrow points to the epithelial wall on the right side.

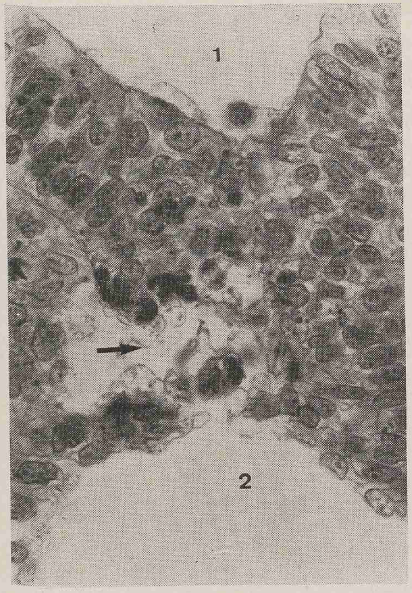

Figure 7. Frontal section of the right nasal cavity (1) of an embryo of 12 mm. Notice the epithelial wall in disorganisation (arrow), the mesenchyme cells do not penetrate the wall, 2 oral cavity.

from penicillin cultures, stregthened our views on the question of cleft genesis. The hadazidine was administered intraperitoneally to rats on the 11th day of pregancy. Fetuses and new-borns showed the same clefts as found in humans.

The phenotype of the cleft varied greatly in its appearance. In some cases it was characterized by a simple cleft of the lip leaving the nasal cavity unaffected *(cheiloschisis),* in others by a complete cleft in which the fissure of the lip was combined with a cleft of the maxillary arch *(cheilo-gnathoschisis).* These forms were often combined with a palatal cleft *(cheilo-gnathopalatoschisis).* These clefts might be like the other forms unilateral or bilateral. The nasal cavity opened deep into the oral cavity, the wing of the nose was flattened on the cleavage side in the case of an unilateral cleft, while the tip of the nose, the septum and the intermaxillary bone were displaced to the normal side. – Often the margins of the cleft were joint together by bridges of fleshy tissue that varied in shape and linked the edges of the cleft in various degree and extension.

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