Craniofacial Characteristics of Cyclopia in Man and Swine

Implications on Role of Medial Structures in Normal Growth and Development

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A rare and bizarre congenital deformity sheds light on the essential function of the nasal septum and other medial structures of cartilaginous origin in the vertical growth of the midface.

Well-controlled orthodontic therapy requires a good understanding of craniofacial growth mechanisms.

The role of the derivatives of the frontonasal prominence in normal craniofacial growth and equilibrium is a critical one. The regulation possibilities vary according to the facial architecture of each species, making comparison of the effects of an otherwise similar malformation in different species very useful in elucidating the nature of normal human growth.

This work investigates the development of cyclopia and its craniofacial manifestations in man and swine. Cyclopia is a rare naturally occurring malformation in which the naso-medial and the paramedial structures of the face are severely impaired or missing.

FREQUENCY OF THE MALFORMATION

Cyclopia has been studied mostly in man. It is extremely rare. *Nishimura et al* (1966) found no reported cases of cyclopia among 100,551 births recorded in hospitals. The same authors studied 3,402 fetuses aged 3 to 10 weeks originating from voluntary abortions, and six cases of cyclopia were found. This indicates that cyclopes rarely come to term; they are usually spontaneously eliminated at an early stage of intrauterine life. The same conclusions are drawn by Matsunaga and Shiota (1977).

Embryology of Cyclopia

Normal development of the face

The face originates from three sources—the neural tube, the frontonasal prominence and the branchial arches (DeMeyer, 1975, 1977).

The neural crest is the precursor of the eyes.

The frontal prominence and the branchial arches are structurally similar. Their ectoderm will give rise to the formation of the teguments, the endoderm to the formation of the mucous membranes of the nose, mouth and pharynx, the mesoderm to the muscles, bones, vessels, and connective tissue.

The frontal prominence develops into the medial facial structures, including the interorbital region, nose, prolabium and all of the medial skeletal structures of the face. Nasal bones, ethmoid, premaxilla and incisors, vomer and cartilaginous septum all develop from the frontal prominence.

From the branchial arches will be produced the lateral segments of the upper face and the mandible. Ears, cheeks, lateral thirds of the upper lip, zygomatic arches, maxillae and hard palate, mandible, associated gums and teeth are all of branchial origin.

Development of cyclopia

Cyclopia is the ultimate expression of a series of anomalies affecting the frontonasal prominence and the medial and paramedial structures that develop from it.

Facial deficiencies may be of varying severity in this spectrum of deformities. The deficit may be only a slight hypotelorism or a slightly hypoplastic nose, nasal bone or premaxilla. In more severe forms, the malformation may extend to a medial facial cleft, of which cyclopia is the extreme form. In cyclopia all of the frontonasal derivatives are missing.

The medial malformations are related to an incomplete organogenesis of the prosencephalon into right and left hemispheres, into olfactive and optic bulbs. It is the lack of cleavage of the prosencephalon into two symmetrical parts that is the basic defect leading to the malformation. The gravity of the medial defect is a reflection of the impairment in prosencephalon development (DeMeyer, *et al.* 1964).

The same impairment as observed in man has been reported in swine cyclopia (Tiedemann, 1926; Favre, 1979). The medial defects of the face and brain, previously called arhinencephaly, are today regrouped under the term of holoprosencephaly, which more accurately describes the nature of the defect (DeMeyer and Zeman 1963).

It is thought that cyclopia starts at the very early stages of development, originating in a primitive deficiency of the prechordal plate (Giroud *et al.* 1963; Cohen *et al.* 1971). The prechordal mesoderm is incapable of producing or inducing normal morphogenesis of the anterior brain and facial structures.

The neural crest is also an important factor in the developmental processes leading to defects in brain and face development (Johnston *et al,* 1974, Johnston, 1975; Hall, 1978). While the skeletal and supporting system of the medial face will develop from the mesoderm of the prechordal plate, as a prerequisite, some cells originating from the cephalic part of the neural crest must invade the mesoderm. These cells migrate into suitable areas and later induce normal frontonasal development.

Similarly, neural cells originating in the midbrain region will contribute to the induction of the first and second branchial arches. This explains why branchial and frontonasal prominence defects may sometimes occur together.

The observed defect may be a consequence of a deficiency in crest cell formation, migration or proliferation; or it may be a consequence of their late differentiation. Any deficiency in the cephalic part of the neural crest will induce alterations of the medial and paramedial structures arising from the frontonasal prominence.

Cyclopia will be the ultimate consequence of a major defect or total absence of the frontal prominence. Patients with a true cyclopia will also have a severely impaired brain and will die in infancy.

Etiology of cyclopia

Etiology of cyclopia (and holoprosencephaly in general) is not yet clearly understood. In most cases the karyotype is normal, although some cases have been occasionally reported in association with more general syndromes like trisomy 18, trisomy 13 or other chromosome anomalies. A polygenic mechanism is possibly involved (Cohen and Hohl, 1976; Matsunaga and Shiota, 1977; Deligdish *et al.* 1978).

Craniofacial Observations in Human Cyclops

Extensive review and detailed descriptions of the abnormalities occurring in cyclopia have been reported in the recent literature (DeMeyer, 1977; Kokich *et al.*, 1982, Mieden, 1982).

All derivatives arising from the frontonasal process are lacking or severely damaged. The ethmoid is missing, as well as the vomer, the whole septum, the inferior turbinate, the nasal bones, the lacrimal bones, the premaxilla and all their associated structures. A rudimentary premaxilla may exist in some cases.

The normally laterally positioned frontal bones and maxillary processes will unite along the midline because of the absence of the ethmoid, nose and premaxilla. The junction between the oropharynx and nasopharynx is obstructed by the joining of the right and left pterygoid plates with the palatal and pyramidal processes of the palatine bones.

The single medial orbit usually contains a single more-or-less rudimentary or subdivided eye.

After union, each maxillary process caries on with the development of its specific structures. There will be neither philtrum nor labial tubercle, which are specific to the frontonasal process. The fact that only one eye develops accounts for the transverse hypodevelopment of the upper jaw.

A small notch should be found in the middle of the lower eyelid. This notch represents a medial lacrimal punctum, located at the union of the two maxillary processes. The presence of this notch is of great theoretical importance, because the lacrimal punctum is a structure inherent in the maxillary processes.

A true cyclop exhibits total arhinia. An homolog of the nose may be present in the form of a penis-shaped soft and blind proboscis, located above the medial eye. This proboscis represents the ultimate residuum of the frontonasal process, and it may contain cartilage. According to Johnston *et al.* (1974), the proboscis is induced by some cells originating from the neural crest. These cells are prevented from migrating into the frontonasal area by the medial orbit, and so are forced to develop superior to the orbit where lack of normal underlying structures leads to formation of a proboscis instead of a nose.

The cyclops mouth is small at least partly because a philtrum and labial tubercle are not present. The four incisors specific to the premaxilla are generally also missing, but some cyclops may show a conical mesiodens. Whether this mesiodens is of branchial or frontal origin has not yet been determined.

Case Reports

Six cases of cyclops are reported here, four human and two swine. They all belong to the Embryology Department of the Faculté de Médecine in Strasbourg.

Human cyclops

All four specimens showed a number of common features (Figs. 1-8). Only derivatives of the frontonasal process seemed to be affected. A nasal structure was not detectable, but a proboscis was present in all cases. One single medial orbit occupied the place of the nasal process. A medial notch was present at each lower eyelid. This notch shows the union of the maxillary processes and the formation of a single orbit with the absence of nasal structures.

Specimens in Figs. 5-8 showed incompletely subdivided ocular processes within the medial orbit. They may be considered as less perfect cyclopes than those in Figs. 1-4.

When the orbital content was too voluminous, it protruded in exophthalmia (Figs. 1 and 5).

The mouth was small and compressed in all cases. Nevertheless, in Figs. 5 and 7 a distinct outline of prolabium and philtrum was just barely discernable. This would suggest that a partial frontonasal induction may have expressed itself in that area.

Facial balance looked relatively acceptable. In all cases the development of the ears looked quite harmonious. This would suggest little or no involvement of the branchial arches in the genesis of the malformation.

Cephalometric evaluations disclosed severe craniofacial malformations (Figs. 2, 4, 6 and 8). In all cases the cranial base was shortened and vertically inclined in its ethmoidal portion. The whole cranial base, including the sphenoidal segment, was severely flattened.

The orbital contents occupied the medial part of the face and seemed to be pushed forward by the flattening of the cranial base. The nasal bone was not visible. The maxillary processes were well developed, and their sagittal and vertical positions in the face were not severely disturbed.

The mandible looked normal in the specimens in Figs. 1-6, which supports the hypothesis of a normal branchial contribution. Mandibular growth was disturbed in the specimen shown in Figs. 7 and 8.

The volume of the buccal cavity appeared too small to match the volume of the tongue in the specimens in Figs. 5-8.

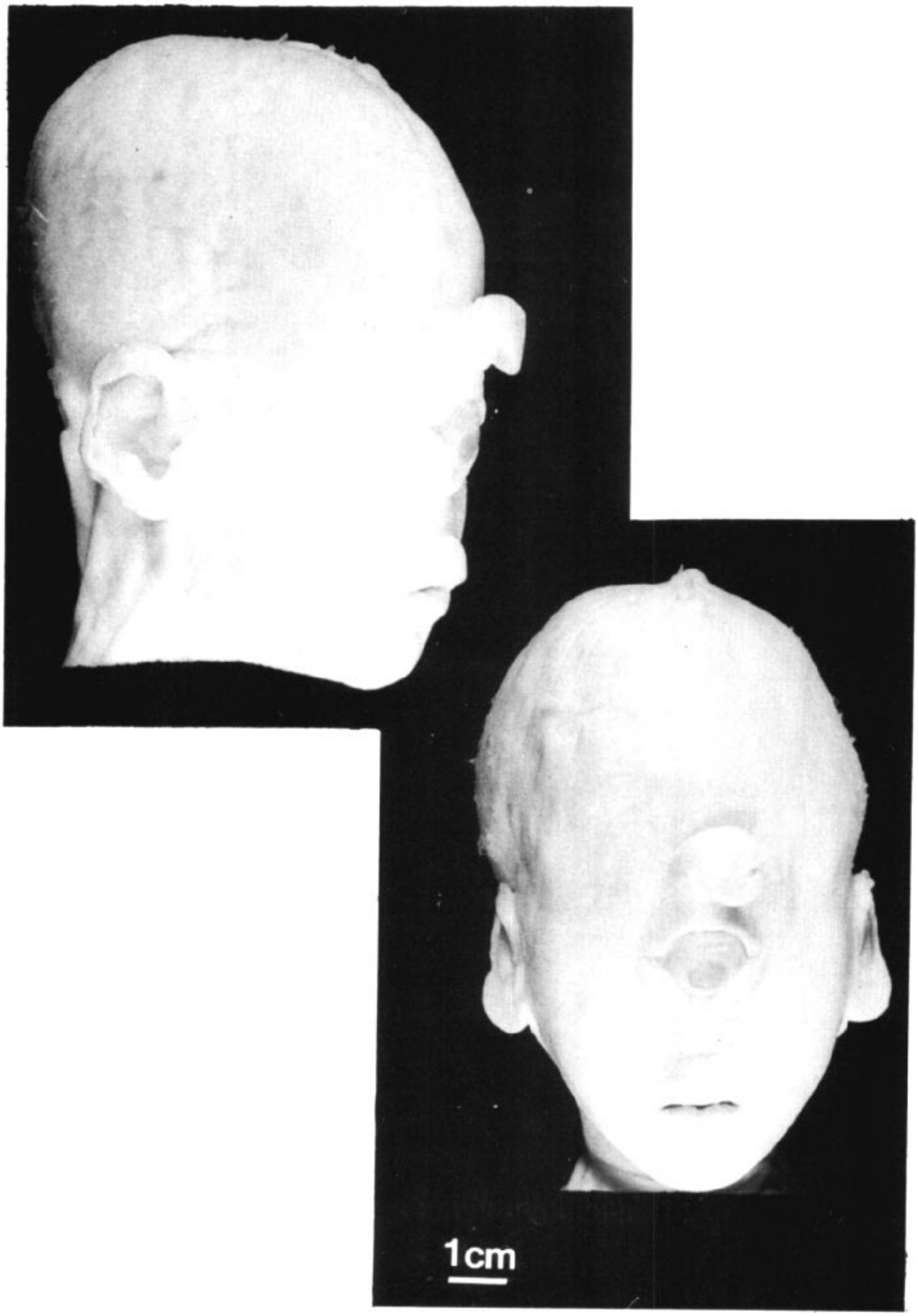

Fig. 1 Face of specimen 1. All external features of cyclopia are observable here. The single eye lies in the middle of the face and no nasal structure can be seen. The mouth is small. There is neither prolabium nor philtrum. The median notch is present at the lower eyelid, and a proboscis stands above the medial orbit. Facial balance is nevertheless acceptable.

Fig. 2 Lateral cephalometric radiograph of specimen 1. The mandible appears to have developed harmoniously. The upper jaw is short (the premaxilla is missing) but does not look distorted. The orbital contents fill the upper face. The cranial base is strongly affected; its anterior segment is shortened and steep, and the whole cranial base looks rounded out to a straighter base angle.

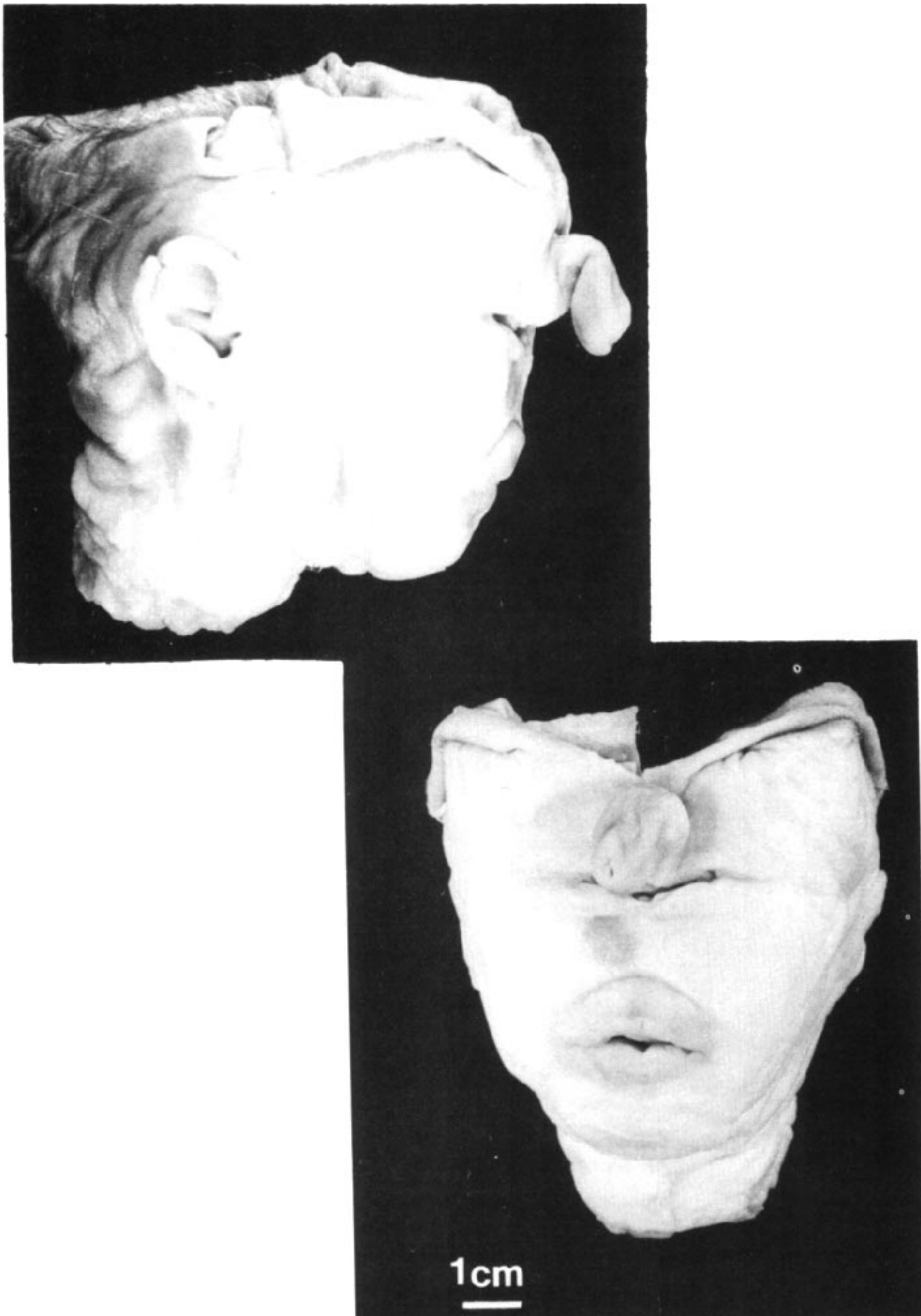

Fig. 3 Face of specimen 2. The brain case had been dissected for autopsy. The orbital contents are less developed than for case 1. Other characteristics are the same.

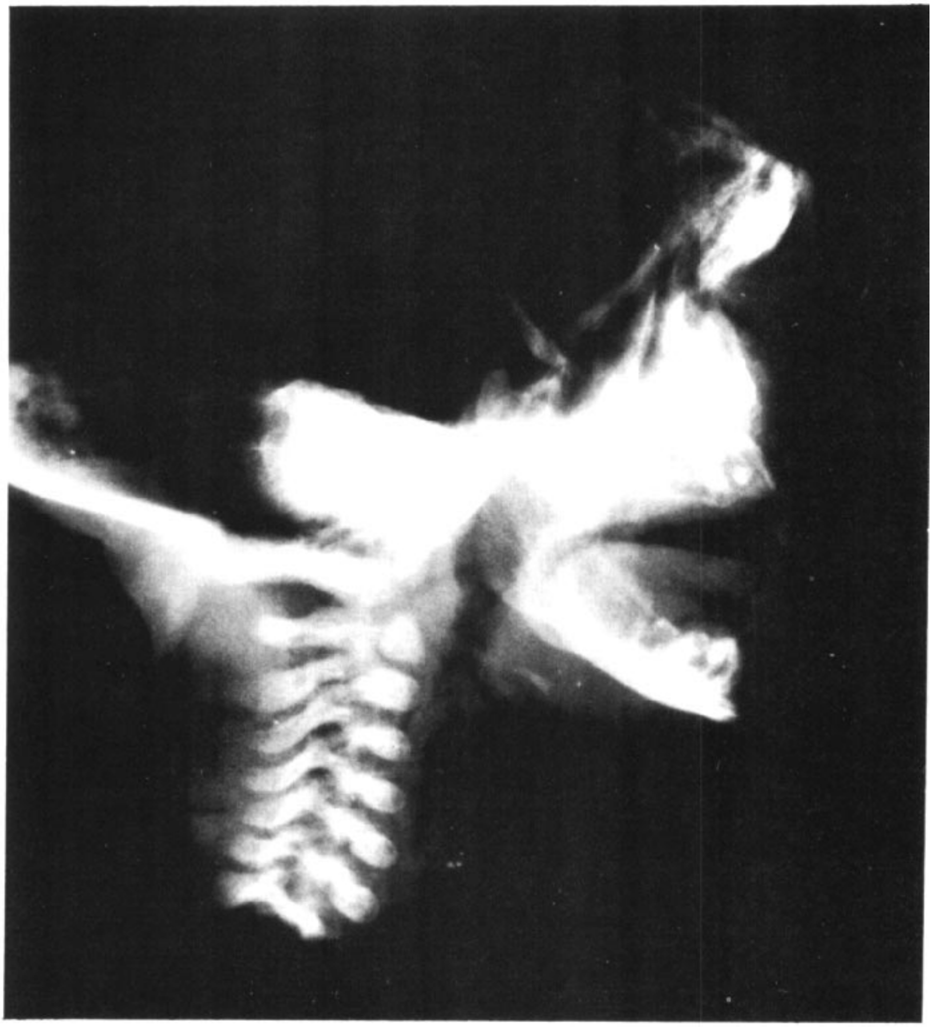

Fig. 4 Lateral cephalometric radiograph of specimen 2. The mandible looks normal. The upper jaw looks almost harmonious in the face. The upper face height equals the vertical dimension of the ocular process. The cranial base is severely affected.

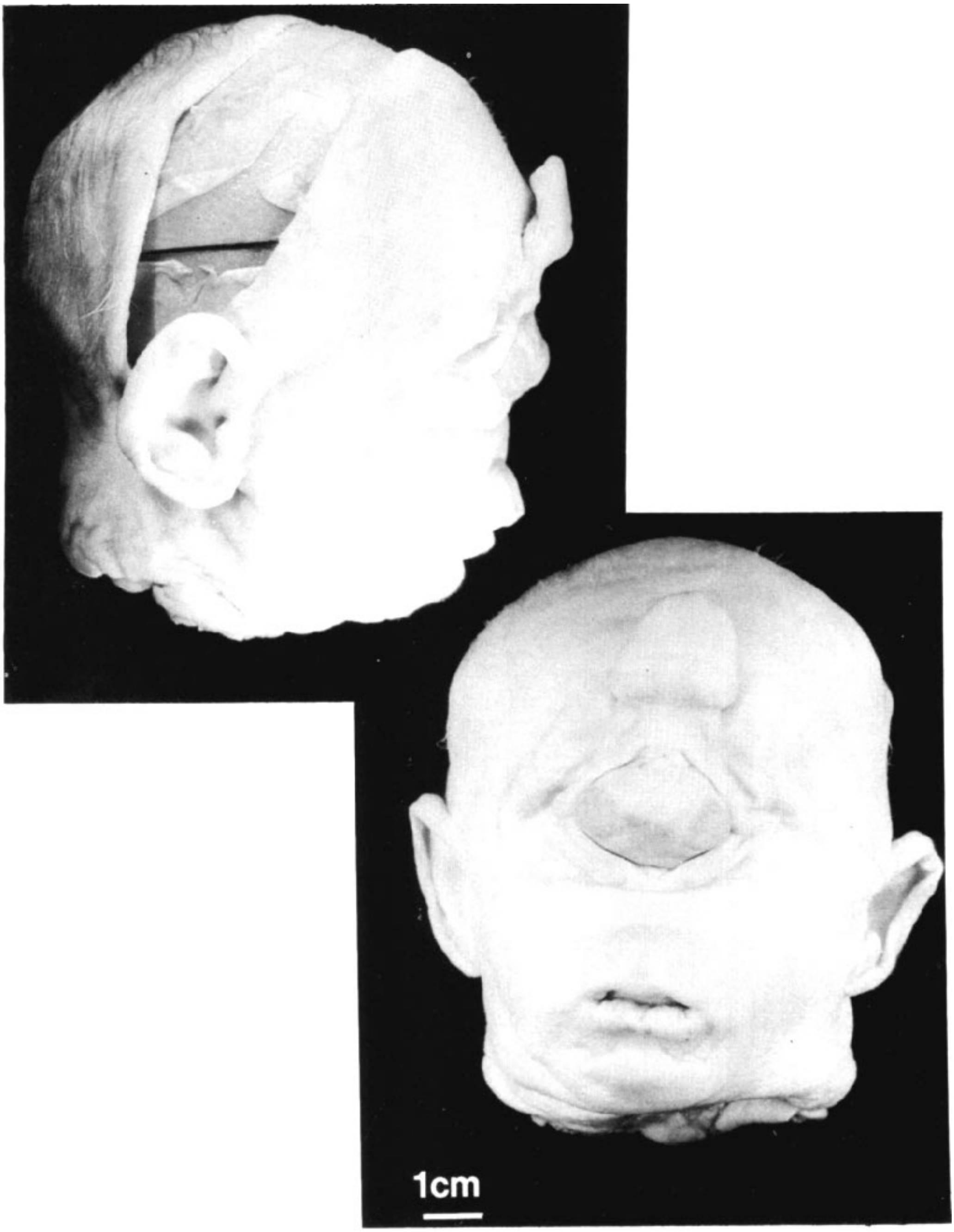

Fig. 5 Face of specimen 3. This case is a less perfect expression of cyclopia than 1 and 2. There are two partly divided eyes within the same orbit. Prolabium and philtrum are slightly visible, indicating a partial expression of the frontonasal prominence in this area. Lower notch and proboscis are present.

Fig. 6 Lateral cephalometric radiograph of specimen 3. The same architecture as in cases 1 and 2 is seen here. The mandible looks normal. The maxilla is supported under the ocular process. The cranial base is flattened to an actual concavity. The tongue is very protruding.

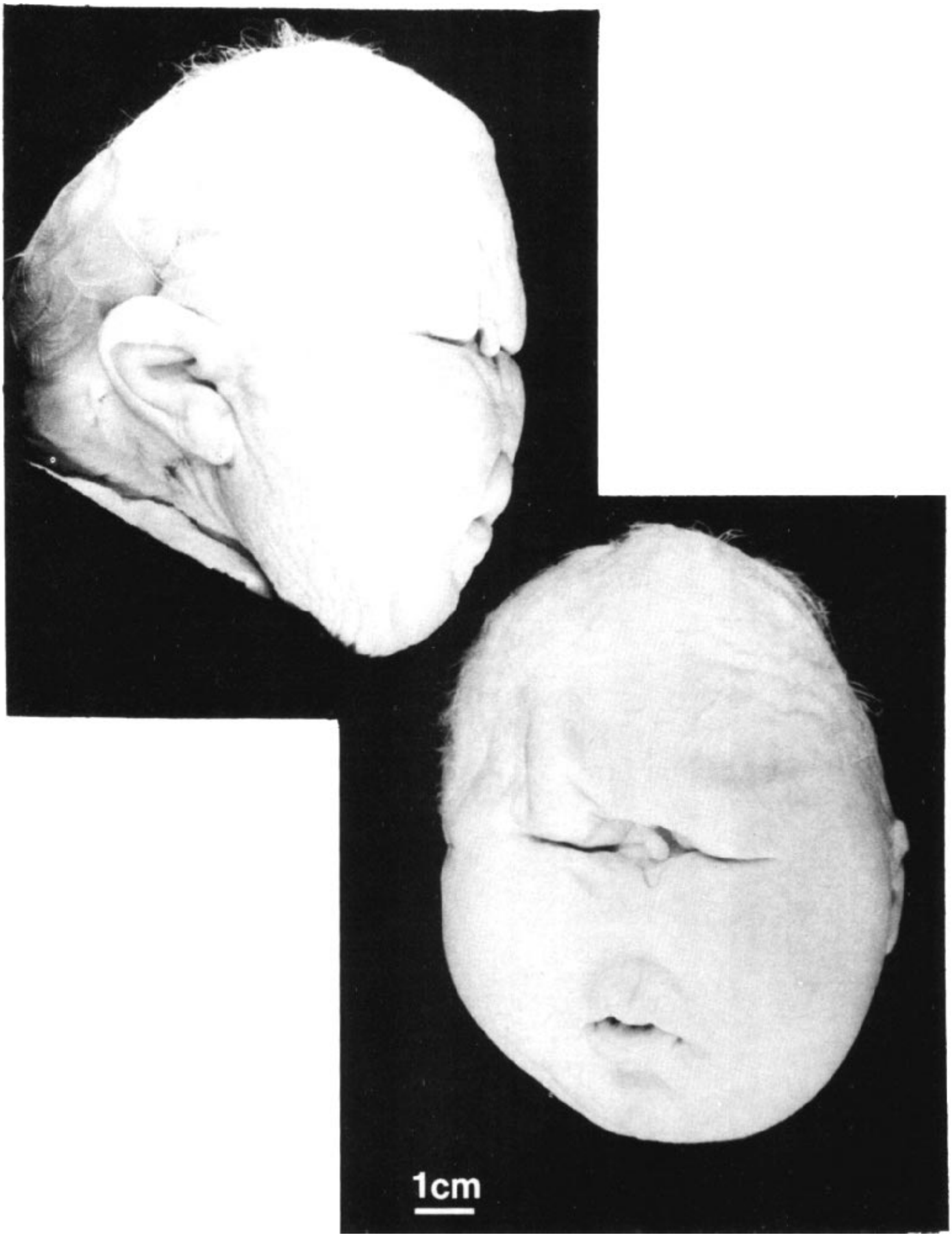

Fig. 7 Face of specimen 4. The median notch at the lower eyelid confirms a true cyclopia with a single orbit. Prolabium and philtrum are present, but no nasal structure is visible. A small proboscis is hanging just at the upper part of the orbit. Brain case is small and heavily affected, and the profile is convex.

Fig. 8 Lateral cephalometric radiograph of specimen 4. Mandibular growth is severely affected. Union between frontal bone and zygoma is not yet completed. The ocular process fills the upper anterior face height. Cranial base is shortened and flattened. The tongue is protruding through the buccal opening.

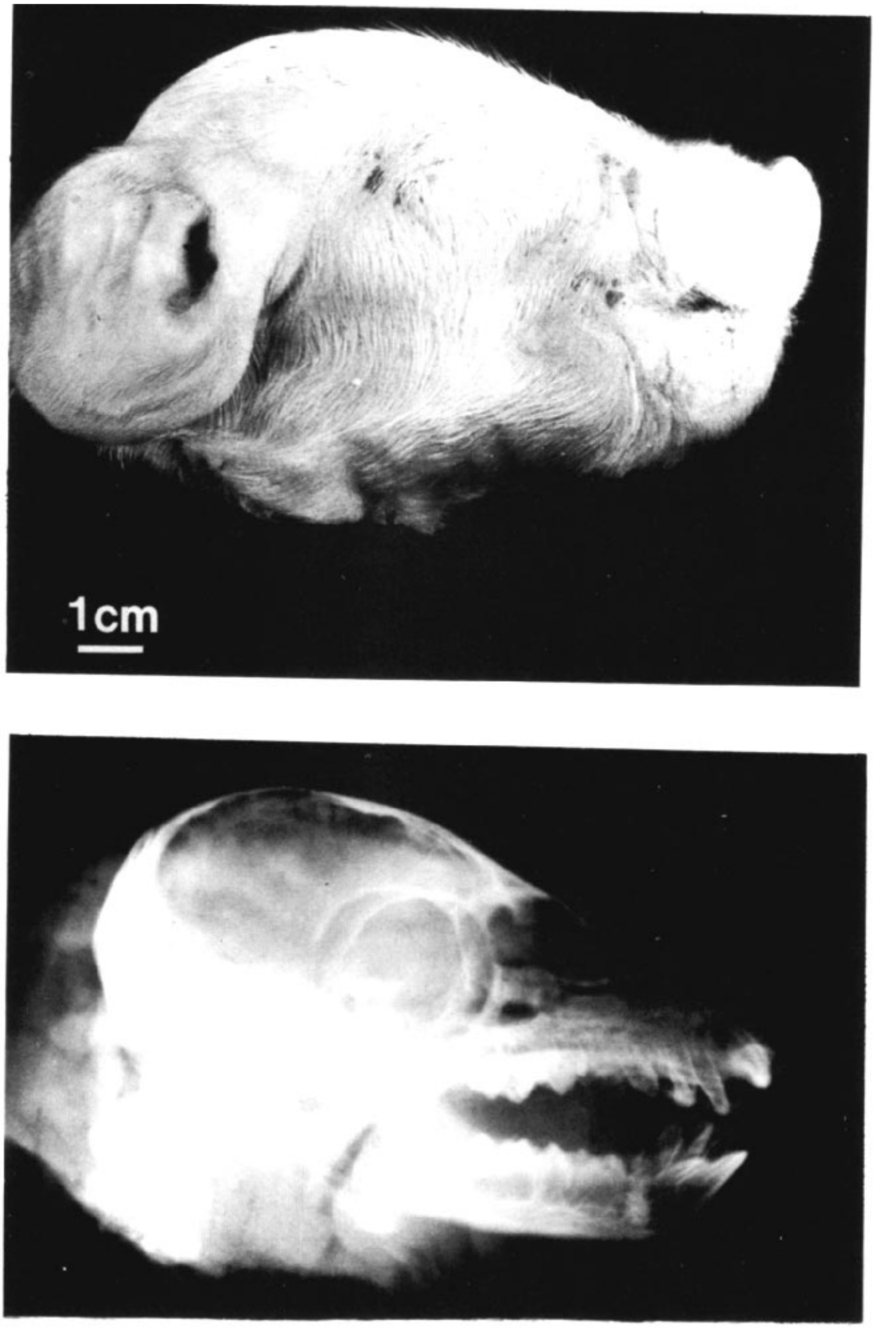

Fig. 9 Normal new-born swine. The face develops in a forward position in relation to the cranium. Nasal and facial structures are sagittally hyperdeveloped compared to their human homologs.

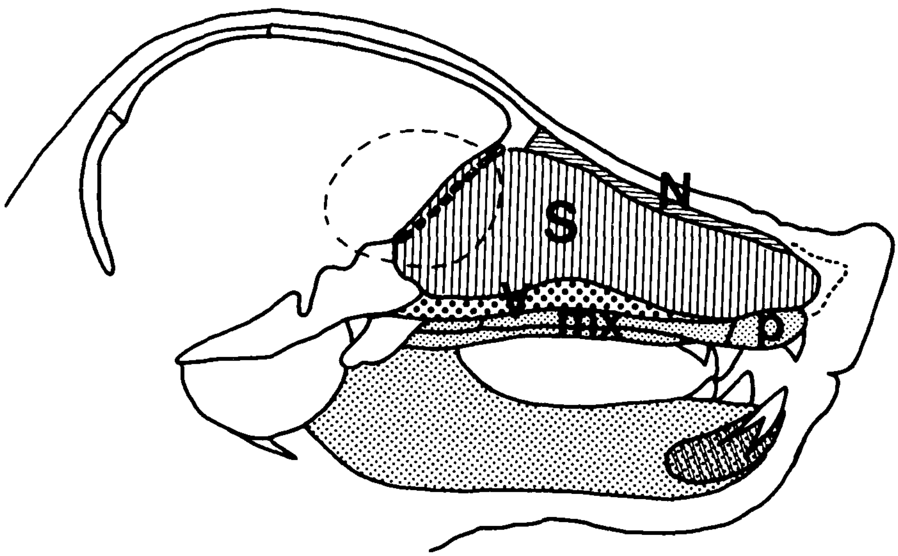

Fig. 10 Parasagittal medial cross section of a newborn swine skull. The homologs of the human face are present, but they develop and protrude anteriorly to the basicranium.

N Nasal bone
S Septoethmoidal process (cartilage at birth)
V Vomer
mx Maxilla
P Premaxilla

The swine cyclops

A normal newborn swine is shown for reference in Figs. 9 and 10. Disfiguration of the two cyclops specimens was the same (Figs. 11-14). The shape of the anterior cranial base was severely affected. The ethmoidal segment looked very steep, and the cranial base tended roughly toward a spherical shape.

The maxillofacial deformation with cyclopia looked much worse in swine than in man, although the same parts of the cranium and the face were affected. The single eye and a proboscis were present, but nasal bones were not seen. The posterior development of the eye was limited by the cranial capsule, so the medial eye had developed in a forward position in relation to the brain case. The inferior border of the orbit surmounted only the very posterior part of the maxilla.

The maxillary collapse was severe. The maxilla was distorted, hypoplastic and tipped upward. The mandible appeared normal. The tongue protruded out of the reduced buccal cavity. The vertical and saggital equilibrium of the face was heavily disrupted.

Discussion

The nasal structures, especially the medial structures, are considered by many authors to have an important influence on the growth of the upper face, yet others consider that the medial septum plays a minor role in

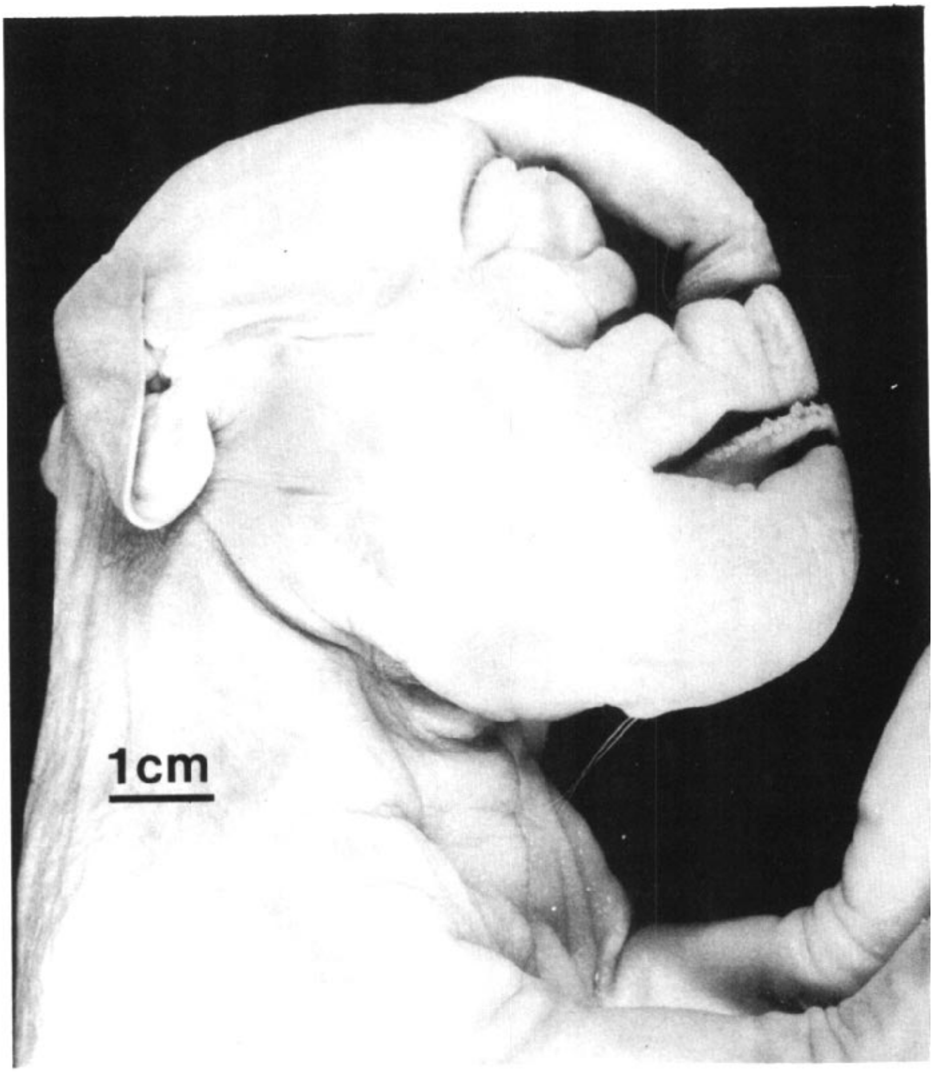

Fig. 11 Face of swine specimen 1. The mandibular development appears normal. The upper jaw is hypotrophic. The upper molars are compressed and crowded. The anterior part of the maxilla is heavily distorted and tipped upward. The cranial base is shortened and rounded. The medial eye has developed in a forward position in relation to the cranial cavity. The tongue is protruding out of the mouth.

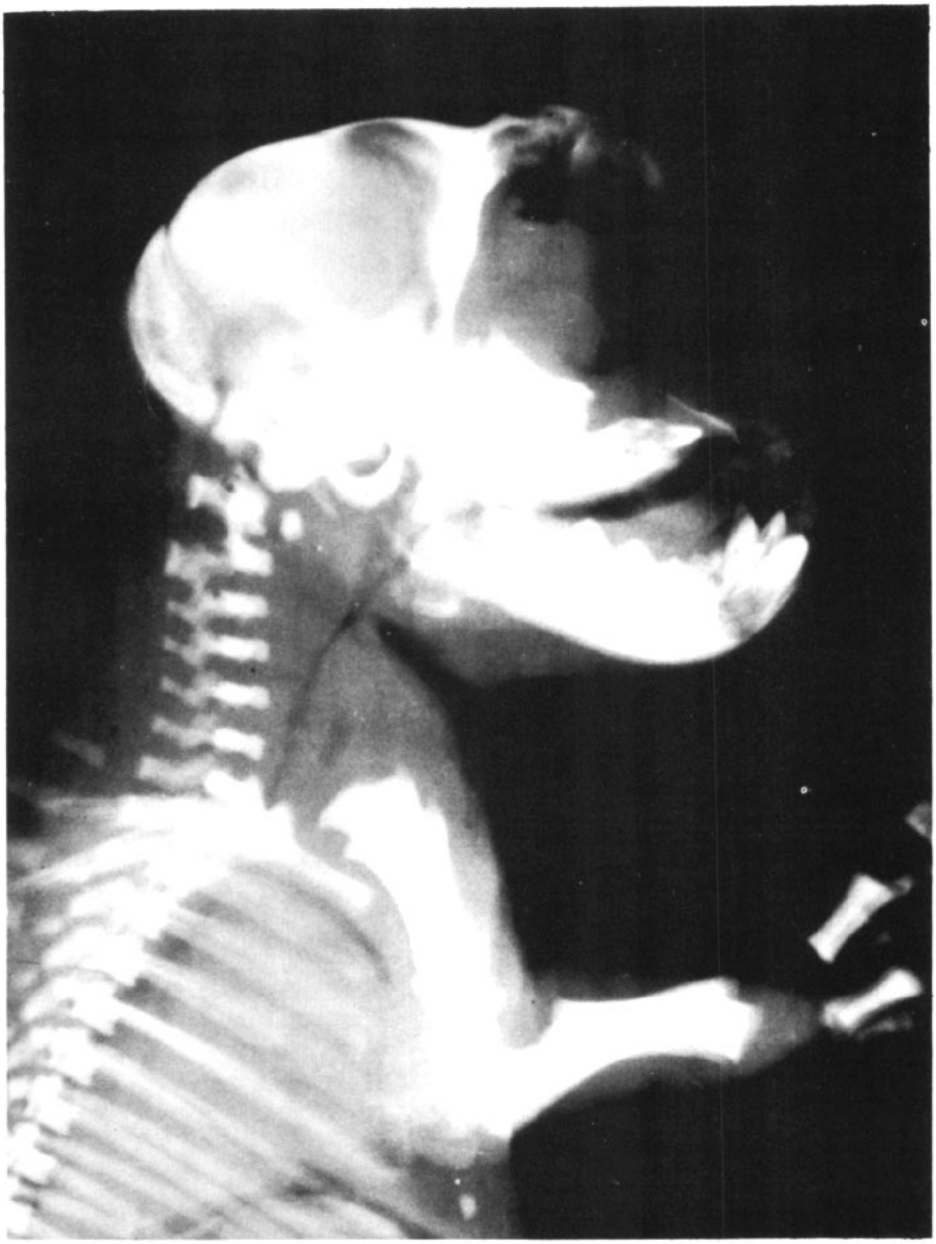

Fig. 12 Radiograph of specimen in Fig. 11.

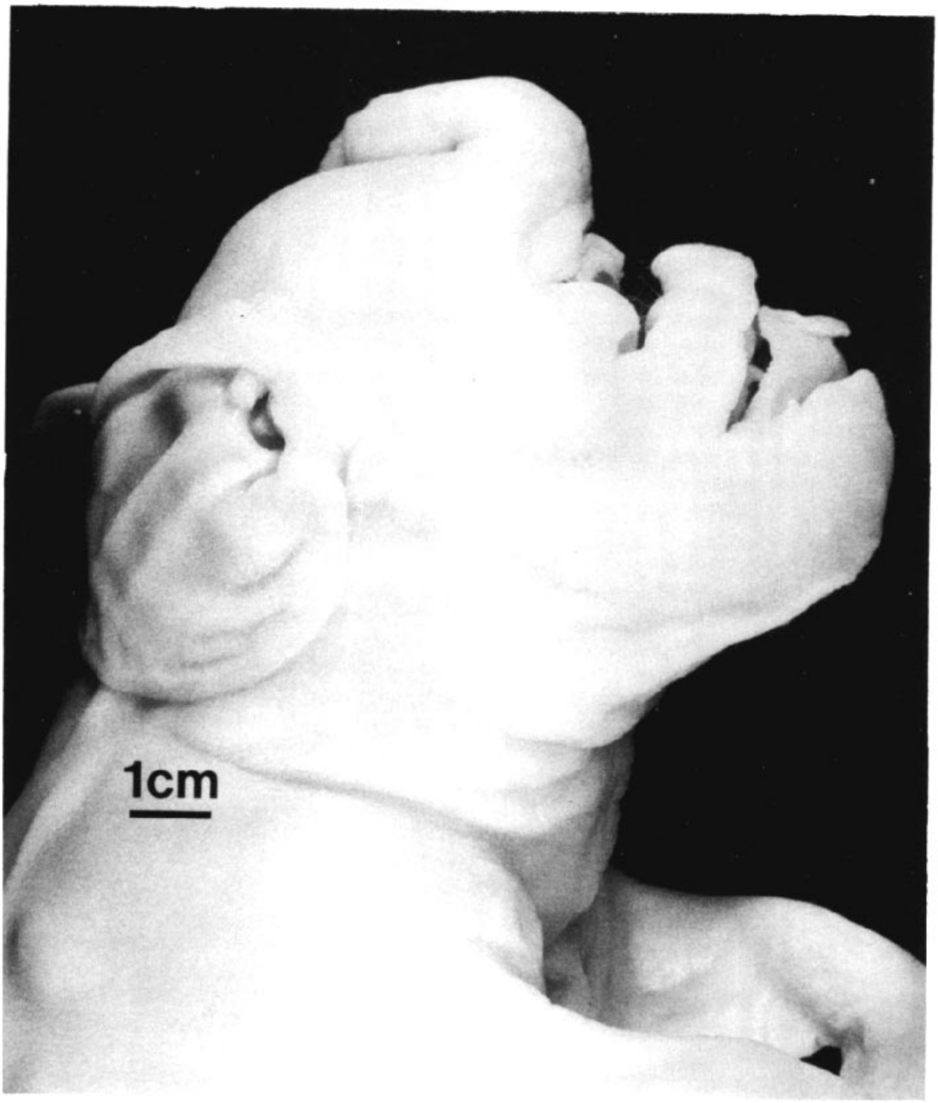

Fig. 13 Face of swine specimen 2. All the observations are similar to Fig. 11.

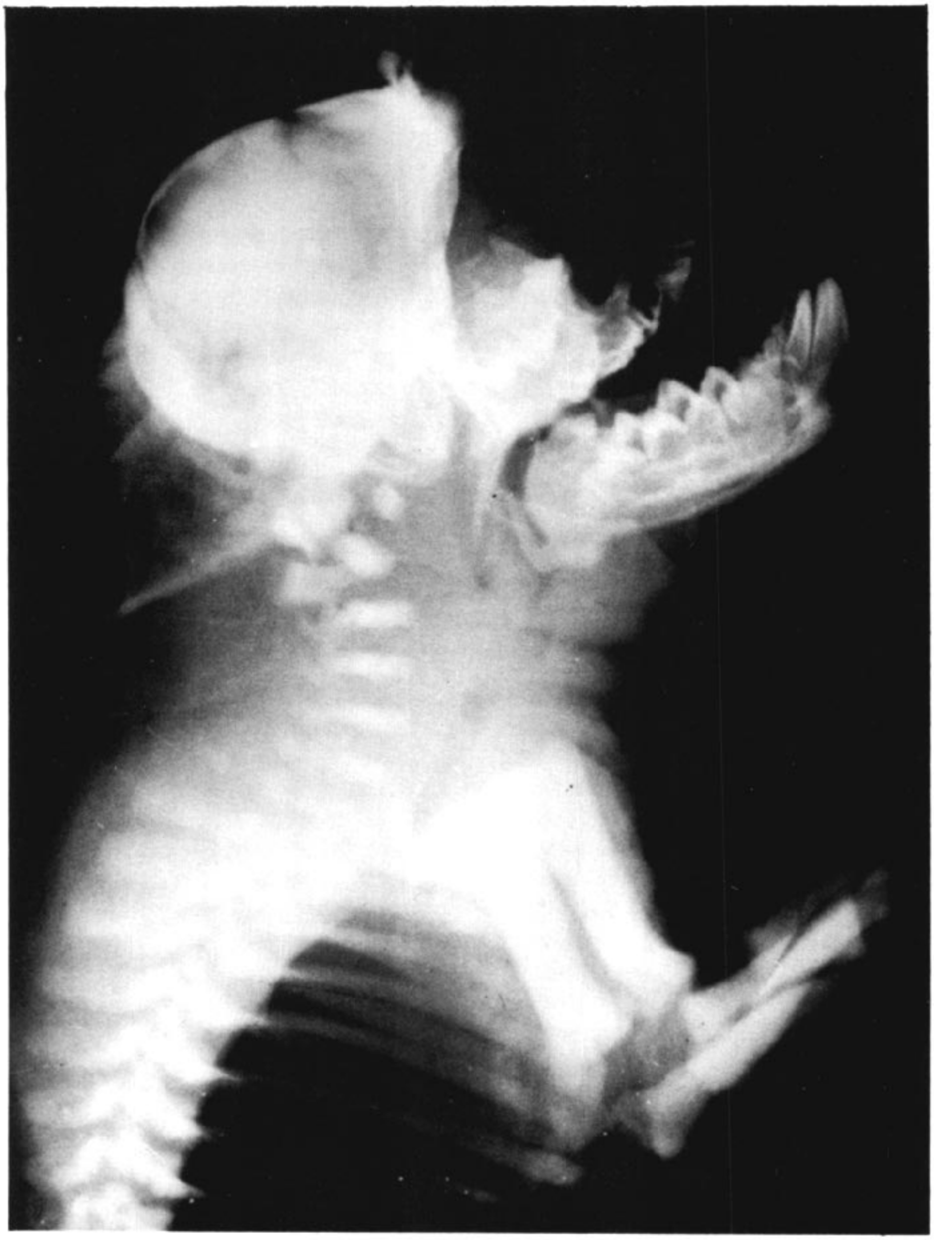

Fig. 14 Radiograph of specimen in Fig. 13.

growth and development of the upper face.

In both species embryological development is basically the same and craniofacial structures are homologous (Patten, 1947, Rugh, 1964). In cyclopia, nasal and medial processes are absent.

Endocranial impairment was similar in man and swine, but facial disfiguration was much worse in swine.

The difference lies in the proportions and organization of the facial components. Examination of the respective architectural characteristics may help to explain the differences found between the effects of cyclopia in the two species.

The cranial base

The cranial base was affected in a similar way in both man and swine. Observation of the cranial base in cyclopes provides important information on the role of the ethmoid bone in normal craniofacial development.

The whole basicranium is of cartilaginous origin. Cartilaginous bone formation is thought to be less sensitive to exogenous or matrix influences than membranous bone formation.

In cyclopia the ethmoid bone is absent, the frontal bones are fused along the midline and the entire anterior part of the cranial base consists of membranous bone.

The basicranium was shortened and seemed to have adapted to the morphogenetic constraints of the growing brain. It can be hypothesized that the cranial base flattened because the expansive force of the growing brain was no longer restrained by a rigid medial structure.

This adaptation has become possible because of the absence of the septoethmoidal process. When the septoethmoial process is in place, it has to be considered as a rigid strut capable of resisting the different strains which are exerted on it. In cyclopia the cartilaginous sphenoid is no longer wedged anteriorly against the ethmoidal strut, so the expansion of the endocranial contents will tend to round out the entire cranial base and impose a forward displacement on the orbital content, which may become more or less extruded.

The flattening of the cranial base and collapse of the sphenoid bone in man may also help push the maxillae forward. In any case, the ethmoidal strut appears to be a major component in developmental equilibrium in the basicranium.

The face

In man, the face normally develops inferiorly to the cranium and seems to emerge from underneath the basicranium. Each maxilla develops under its overlying orbit.

The vertical dimension of the upper face corresponds to the height of the septal structures. Only the tip of the nose protrudes from the normal face.

In human cyclopia, the ocular process occupies the medial part of the face, where the orbit is limited posteriorly and superiorly by the anterior cranial fossa. The orbital floor corresponds to the palatal roof instead of the maxillary sinuses. The whole upper face is filled with the ocular structures.

The vertical height of the upper face, which normally corresponds to the height of the medial septal structures, is now reduced to the height of the orbit. This vertical collapse can only be minor, because the two maxillae and their palatal processes join and develop under the medial eye. It is likely that in human cyclopia the development of the orbital matrix governs the upper face height and at least partly stimulates maxillary growth and adaptation.

In swine, the relative importance of the facial structures is very different. At birth, all normal swine show the same configuration (Bourdelle, 1920). The snout develops far forward. The jaws protrude in relation to the cranial base. Nasal structures, including medial septum, are sagittally hyperdeveloped in comparison to their human homologs.

Only the very posterior part of the maxilla is sheltered under the anterior part of the cranium in the normal swine.

The maxillofacial manifestations of cyclopia in swine are very severe. The maxillae are heavily distorted and hypoplastic. The anterior segment, with no structures to support it, is tipped upward. In this situation the oculo-orbital development cannot act as a support to maintain the vertical height of the upper face.

This indicates that the maxillary collapse in swine is closely related to the absence of a rigid medial strut. The role of the septoethmoidal process as a medial frame is of the utmost importance. Clearly in swine the medial structures are of prime necessity to a harmonious equilibrium of the basicranium and also the entire upper face.

Conclusions

The development of the cranial base is strongly affected in cyclopia, due to the absence of the ethmoid frame. The basicranium was shorter and seemed to have adapted partly to the morphogenic influence of the growing brain. This adaptation was similar in man and swine.

On the other hand, the maxillofacial manifestations of cyclopia were quite different in the two species.

In man, the face develops underneath the basicranium and in human cyclopes the medial eye helped maintain a vertical equilibrium in spite of the total absence of a medial septum.

In swine, the face develops in front of the cranium, and with all medial septal structures missing, there was a severe collapse and distortion of the upper jaw.

These observations support the hypothesis that in normal craniofacial growth the medial septal structures of cartilaginous origin act as an indispensable strut in the growth and development of the face.

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