Virchows Arch. path. Anat. 339, 245—253 (1965)

From the Department of Pathology, Dartmouth Medical School
Hanover, New Hampshire U.S.A.

Study of the sphenoid bone in human cranioschisis and craniorhachischisis*

By
M. Marin-Padilla

With 6 Figures in the Text

(Received January 4, 1965)

Introduction

A disturbance in the axial cephalic mesoderm occurring before the closure of the anterior neuropore has been suggested [Marin-Padilla (1)] as a possible cause of cranioschisis (anencephaly) in man. The affected cephalic mesoderm fails to enclose the cephalic portion of the neural tissue and constitutes an abnormal skeleton for the base of the skull. The skeletal components of the head in cranioschisis are affected differently resulting in three distinct types of abnormalities. The malformations of the cranial vault bones are to be expected in cranioschisis since a completely formed neurocranium in these infants never existed. The facial bones, which in general are not primarily affected in cranioschisis, have abnormal positions or shapes which they assume secondarily in their adaptation to the abnormal skeleton of the base of the skull. The bones of the base of the skull on the other hand are primarily affected in cranioschisis and reflect the underlying primary disturbances of the axial cephalic mesoderm.

The concept of a primary mesodermal condition as a cause of cranioschisis has been recently substantiated by both clinical [Marin-Padilla (2)] and experimental observations (Marin-Padilla and Ferm). Necrosis of the cephalic somites was found in embryos with experimentally induced cranioschisis which precede any appreciable change in the neural tube or in the notochord.

The mesodermal disturbance leading to cranioschisis in man may be due to a necrosis of somites, a possibility which has not been investigated. The malformations of the bones of the base of the skull, which are primarily affected in cranioschisis, may reflect a pre-existing segmental or somitic disturbance. In view of this possibility the sphenoid bone was selected for the present study because of its central position in the base of the skull and because it has been considered to be [Marin-Padilla (1)] the most typically affected bone of the skull in human cranioschisis.

The purpose of this study is to report the results of an analysis of the sphenoid bones of five cases of human cranioschisis and craniorhachischisis with different degrees in the severity of their malformations. The sphenoid bone is expected to be similarly malformed in these cases, regardless of the severity of the schisis and the extent of the degeneration of the nervous system. This is expected if its malformations are the result of a segmental or somitic injury rather than the result of a primary disturbance in the neural tissue, the concept generally accepted today.

* This work was supported by United States Public Health Grant GM 10210.

Material and Method

Five cases of human cranioschisis and craniorhachischisis, from the author's collection, were selected for this study. These cases were elected because they represent five forms of the malformation with an increasing severity in their defects including the less and the most severely affected forms. For the purpose of the present study these cases will be identified as cases # 1, 2, 3, 4 and 5. Case # 1 presents a partial anterior cranioschisis. This case represents one of the less affected forms, and has a partially formed occipital bone. The brain is degenerated except for a small portion of the cerebellum and medulla, which are preserved because they are enclosed and protected by bone. Case # 2 presents a complete simple cranioschisis. The brain is totally degenerated, there is no foramen magnum (occipital schisis) and the first and second cervical vertebrae show an occult rhachischisis. Case # 3 presents a cranioschisis with a complete open cervical rhachischisis. The brain and cervical spinal cord are totally degenerated. Case # 4 presents complete cranioschisis and rhachischisis (craniorhachischisis totalis) and the entire brain and spinal cord are degenerated. Case # 5 is an example of the most severely affected forms of this malformation. It presents a craniorhachischisis totalis with a pronounced cervico-dorsal lordosis, and anterior dorsal rhachischisis, a large diaphragmatic hernia and a large omphalocele. The trunk and abdomen in this case are severely malformed and numerous rib abnormalities are also present.

The sphenoid bones of the above cases were obtained by the following procedure: dissection of the soft tissue of the head, boiling of the skeleton of the head followed by careful dissection of the remaining soft tissue until the bones can be easily separated. Great care was taken not to disturb, by boiling or by dissection, the architecture and configuration of the bones. The superior and slight anterior aspect of all the sphenoid bones (depicted in figures) was selected for photography because it is the most representive of the bones and shows best the malformations.

Observations

Normally, the sphenoid bone at birth consists of three portions: a central one composed of the body and the two lesser wings, and two lateral portions each formed by a greater wing and its corresponding pterygoid process. In cranioschisis and in craniorhachischisis the sphenoid bone consists of a single piece. The bone also has an abnormal position in the base of the skull being posteriorly rotated in such a way that the angle formed between its basilar portion and that of the occipital bone is larger than normal.

The general description of the malformations of the sphenoid bone which follows is applicable to each separate bone since all are similarly malformed. In this description the term cranioschisis is used to include the two forms of the malformation studied (cranioschisis and craniorhachischisis). Arbitrarily, for the purpose of this description the sphenoid bone is considered to be divided into five portions. Each of these portions corresponds to an anatomical feature and is characteristically affected in cranioschisis. The five portions are: the body of the sphenoid (*A* in all figures), the lesser wings (*B* in all figures), the greater wings (*C* in all figures), the pterygoid processes (*D* in all figures) and the rostrum (*E* in all figures). Each of the above portions is described separately and a general view of the bone as a whole will follow. To facilitate the description and for a better understanding of the abnormalities, the sphenoid bone of a normal newborn infant is depicted in Fig. 1. Figs. 2, 3, 4, 5 and 6 depict the sphenoid bones of the 1st, 2nd, 3rd, 4th and 5th cases respectively.

The body of the sphenoid bone in cranioschisis (*A* in all figures) is thicker and narrower than normal. The sella turcica is shallow, poorly formed and in some cases practically absent. The carotid grooves are present in both sides of the body. The surface which articulates with the occipital bone is not the posterior aspect of the body as is normal, but the postero-inferior surface. The abnormal position of this articular surface gives the impression that the sphenoid bone and the

occipital bone are almost at the same plane. The inferior and posterior surfaces of the sphenoidal body are small and angulated. The rostrum occupies the anterior surface of the sphenoidal body (Figs. 2—6).

The lesser wings (*B* in all figures) of the sphenoid bone are severely affected in cranioschisis. They are reduced to mere bony arches enclosing the optic foramina. The optic foramina have normal diameters in all cases. The most prominent abnormality of the lesser wings is the marked reduction of their transverse diameter. The ethmoidal spine located anteriorly and between the lesser wings, which normally is a cartilaginous structure at birth (the anterior empty space between the lesser wings in Fig. 1) is prominent and well ossified. It appears as a portion of the rostrum and cannot be separated as a distinct structure from it (Figs. 2—6).

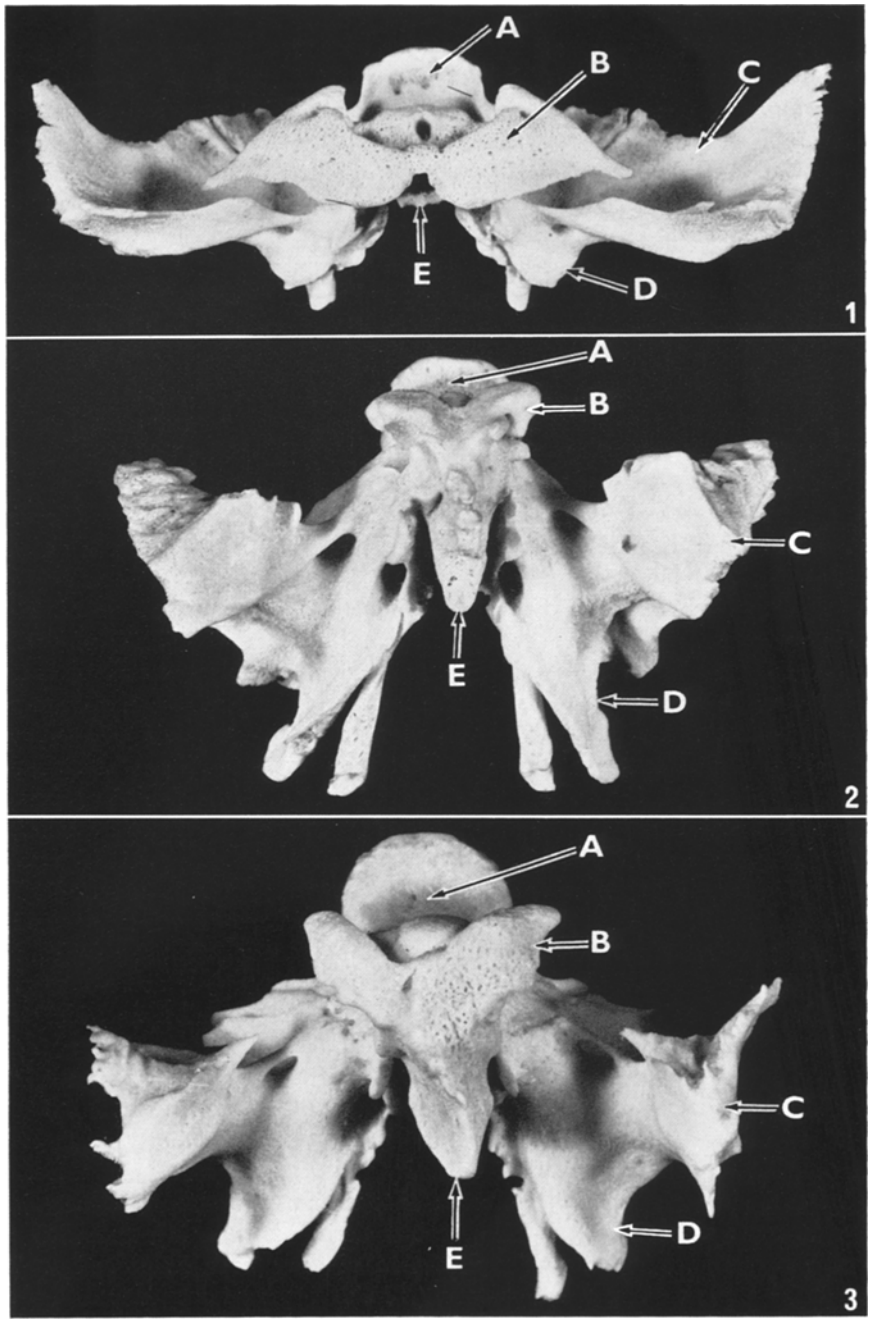
The greater wings of the sphenoid bone (*C* in all figures) in cranioschisis appear folded. The superior surfaces (Fig. 1) are irregular and smaller such causing a reduction in the size of the middle cerebral fossa. The foramina rotundum and ovale of the greater wings are present and within normal limits. The spines angularis are well formed. The lateral margins and the distal portion of the wings are thick, crude and irregular. The transverse diameter or the span of the greater wings markedly reduced (Figs. 2—6).

The pterygoid processes of the sphenoid bone (*D* in all figures) in cranioschisis are typically malformed in all cases. They are larger, thicker and longer than normal. The length of the medial plate of the pterygoid process decreases in direct proportion to the increase in the severity of the malformation (compare the length of the medial plate of the pterygoid process in Figs. 2—6). The pterygoid processes are markedly deviated anteriorly and laterally assuming an oblique position with the greater separation at their distal ends. The pterygoid canals located at the base of each pterygoid process, normally very small, in cranioschisis are rather large. The pterygoid canals are the large foramina at the base of the pterygoid processes seen on each side of the rostrum (Figs. 2—6).

The rostrum (*E* in all figures) of the sphenoid bone shows the most outstanding abnormality of the bone in cranioschisis. Normally, at birth the rostrum is a cartilaginous crest located in the inferior surface of the sphenoid bone (Fig. 1). In cranioschisis, the rostrum is a large ossified crest deviated anteriorly and occupies completely the anterior aspect of the bone. It is prominent and considerably larger and thicker than normal. It is usually tortuous or deviated laterally. It cannot be separated anatomically from the anterior ethmoidal spine (Figs. 2—6).

The sphenoid bone as a whole is identically malformed in all cases studied. Its transverse diameter is markedly reduced due to the narrowness of the lesser wings, the greater wings and the body. Its antero-posterior diameter is increased due to the abnormal rostrum and to the deviation of the pterygoid processes. The outstanding malformation of the rostrum (*E* in all figures) characterizes all of the sphenoid bones studied. The bones lack an orbital fissure but all the other anatomical foramina for vessels and nerves are present.

Minor variations from the above general description of the sphenoid bone can be recognized easily in a comparative analysis of all cases (Figs. 2—6). However, there are no major deviations from the basic defects described. One interesting



Figs. 1—6. Key To the Figures: *A* The body of the sphenoid bone. *B* The lesser wings. *C* The greater wings. *D* The pterygoid processes. *E* The rostrum

Fig. 1. Anterosuperior aspect of the sphenoid bone of a normal newborn infant. ×1.8. Fig. 2. Anterosuperior aspect of the sphenoid bone of a newborn infant with a partial anterior cranioschisis. ×2. Fig. 3. Anterosuperior aspect of the sphenoid bone of a newborn premature infant with a complete simple cranioschisis. ×2.5

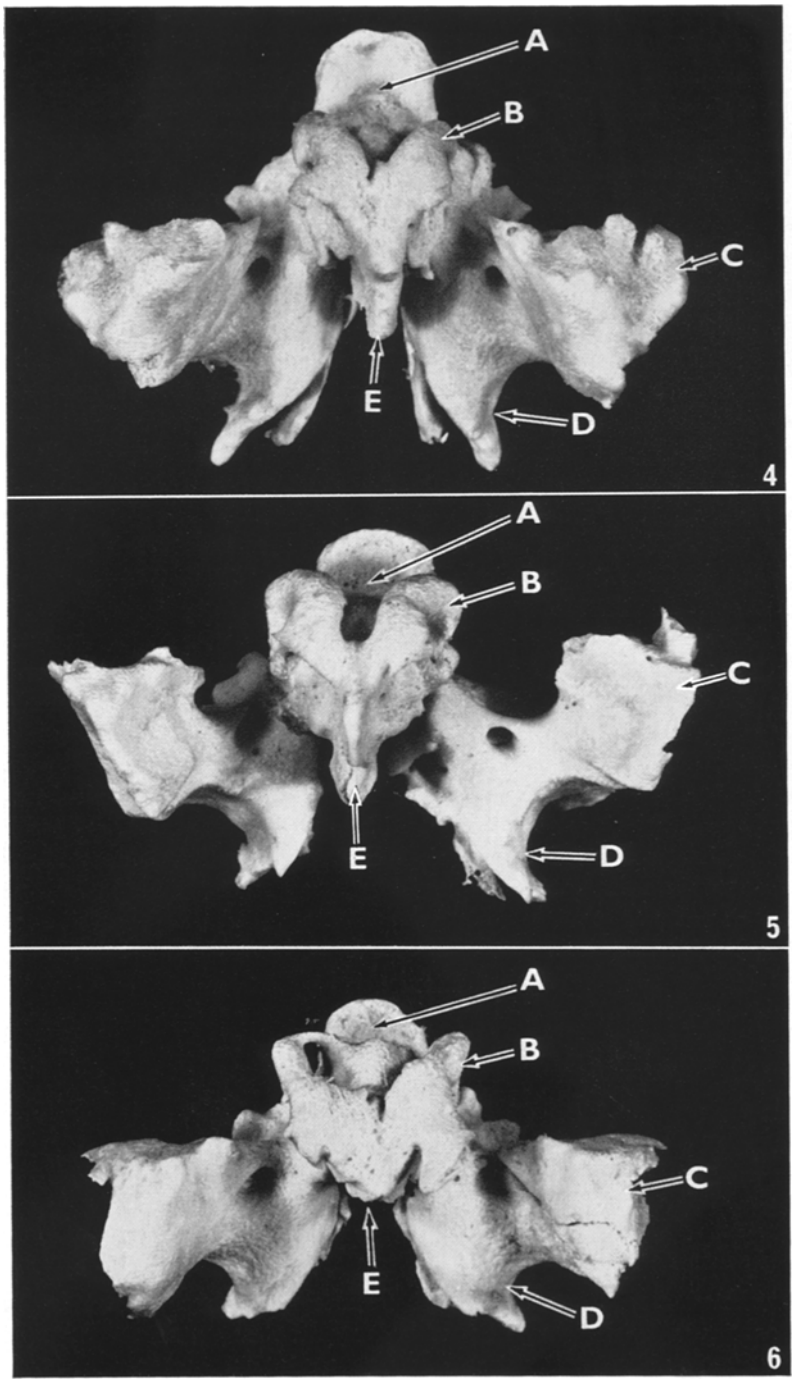


Fig. 4. Anterosuperior aspect of the sphenoid bone of a newborn premature infant with a partial craniorhachischisis (cervical rhachischisis). ×2.5. Fig. 5. Anterosuperior aspect of the sphenoid bone of a newborn premature infant with a craniorhachischisis totalis. ×3. Fig. 6. Anterosuperior aspect of the sphenoid bone of a newborn infant with a craniorhachischisis totalis, an anterior dorsal rhachischisis, a diaphragmatic hernia and a large omphalocele. ×3

variation is that the crude appearance of the entire bone increases in direct proportion to the increase in severity and extent of the malformation. Compare the sphenoid bone of the less affected case (Fig. 2) with the bone of the most severely affected case (Fig. 6). The intermediate forms (Figs. 3, 4 and 5) show different gradations in the appearance of their bones from the less to the more severely affected cases.

The malformed sphenoid bone in cranioschisis affects the configuration of the skeletons of the head and face. This is due to its central position in the skeleton of the head and its articulation with twelve other bones of the head and face. The positions of the vomer bone, the palatine bones and the zygomatic bones are abnormal because they articulate with an abnormal sphenoid bone. A direct consequence of the abnormal position of the vomer bone and palatine bones is the position of the maxillae which are equally affected. The anomalous positions of these facial bones are secondary to the abnormal rostrum and position of the pterygoid processes of the sphenoid bone. Of a particular interest in this regard is the typical malformation of the maxillae (high ogival palate) encountered in cranioschisis which appeared to be directly related to the abnormality of the sphenoid bone. First, the prominent rostrum of the sphenoid bone is the cause of an abnormal elevation and deviation of the vomer bone. Second, the oblique separation of the pterygoid processes with its greater separation toward their distal ends, is the cause of an oblique position of the palatine bones leading to narrowness and ogival shape of the choanae. Third, the position of the maxillary bone, especially its palate portion, is affected by the position of the palatine bones adopting a high ogival position. The maxillae also have a very narrow palate. The ethmoid bone, which is severely malformed in cranioschisis, is primarily affected by the axial mesodermal disturbance and perhaps secondarily by the abnormal ethmoidal spine of the sphenoid bone. Other bones of the head known to be primarily affected in cranioschisis (incompletely formed neurocranium) such as the frontal bones, the temporal bones and the parietal bones also assume abnormal positions from their articulation with the abnormal sphenoid bone.

Discussion

The study of the sphenoid bone of human cranioschisis and craniorhachischisis has shown: First, the bone is equally affected (malformed) in all cases studied regardless of the extent of both the malformation and the degeneration of the nervous tissue. Second, the malformations found in the sphenoid bones support the concept of a basic disturbance in the axial cephalic mesoderm as their more likely cause. Third, the similarity in the defects of the sphenoid bones studied favors the concept of a primary mesodermal disturbance *common* to all forms of these malformations. Also, it suggests a possible segmental nature in the primary axial mesodermal disturbance.

The malformations of the sphenoid bones described above do not support the classic theories of the morphogenesis of cranioschisis. The classic concept (STERNBERG; FELLER and STERNBERG) and most generally accepted today, is well expressed by the following statement of WILLIS: "The non-development of the calvarium (acrania or cranioschisis) in anencephaly is not merely a failure of closure, but a total failure of development of the primordia of the bones of the

skull vault. This is almost certainly a consequence of the non-development of the brain". The above concept supported also by MATHIS and DEPPE considers a primary disturbance in the neural tissue to be the cause of the skeletal malformations. The above authors give little attention to the malformations of the bones of the base of the skull and concentrate their attention on the bones of the cranial vault. However, all the bones of the cranial vault are present in cranioschisis (WEINHOLD; AUGIER; DE BEER; MARIN-PADILLA). It is true that some of these bones are only represented by small fragments, but these fragments are always identifiable by their articulations with other less affected bones. The malformation of the cranial vault bones merely reflects the lack of formation of a complete neurocranium. This lack of formation of a complete neurocranium is supported by experimental observations (GIROUD and MARTINET). Also, WEINHOLD contends that in anencephaly (cranioschisis), the origin of the bones of the cranial vault is not dependent on the brain but that their growth and morphologic differentiation is indeed dependent. DE BEER agrees with WEINHOLD's contentions and adds that in anencephaly the bones of the base of the skull, which are not dependent on the brain are "fairly normal, as are those of the face". Of course, if this were to be the case the morphogenesis of anencephaly becomes a simple matter of lack of induction: absence of brain (anencephaly) causing absence of cranial vault (cranioschisis). This concept has prevailed and it has become the most generally accepted one. However, the existence of typical malformations in the bones of the base of the skull in cranioschisis (MARIN-PADILLA) invalidates the above concept of the embryogenesis of this malformation.

It can be stated that the first established defect in cranioschisis (V. RECKLINGHAUSEN) is a failure of closure of the cephalic region of the neural tube. If one considers a primary failure of closure of the neural tube, it will necessarily be accompanied by a defect in the dorsal cephalic mesoderm. This defect later in embryonic development will cause a schisis in the neurocranium explaining the malformations on the cranial vault bones. On the other hand, if the primary disturbance (schisis) occurs in the dorsal cephalic mesoderm, it also will be accompanied (in early embryonic stages) by a defect (schisis) in the cephalic neural tube and it will result in the same type of malformations in the bones of the cranial vault.

The mesodermal disturbance considered to be the cause of cranioschisis is required to affect both the dorsal and the axial cephalic mesoderm and to occur early in embryonic development. This mesodermal condition will affect the dorsal mesoderm which then fails to enclose the neural tube, and will also affect the axial cephalic mesoderm resulting in an abnormal skeleton for the base of the skull. The brain which is left uncovered and without proper lodging degenerates secondarily. The degeneration of the exposed segments of the neural tube appears to begin at their most dorsal areas which are exposed earlier, thus permitting the ventral centers to develop normally for some time. The eyes and the main nerve trunks will develop normally and that will help to explain the normal eyes and nerves encountered in cranioschisis with totally degenerated brains. The mesodermal disturbance considered above as the cause of cranioschisis can be the result of somite alterations. This is believed to be true for these reasons. First, the

somites precede the closure of the neural tube and they actively intervene in its closure (dermatomes) and in its support and lodging (sclerotomes). Abnormalities of the somite on the other hand can cause defective closure and lodging of the neural tube. Second, somite alterations may lead to segmental disturbances in the mesoderm which may be reflected in the malformations of the affected structures. The similarity in the malformations of the sphenoid bones of differently affected cases of cranioschisis, presented here, supports this view. Third, in experimentally induced cranioschisis, cellular necrosis of somites of the cephalic region was encountered. These necrotic changes preceded any appreciable alterations in the neural tube.

Some of the experimental investigations on the pathogenesis of induced cranioschisis require a few comments. GALLERA encounters somite alterations (duplication, triplication and abnormal positions) in very young chick embryos with platyneuria (craniorhachischisis) induced by oxygen deficiency. He considers that disturbances in the chordo-mesodermal material during the formation of the primitive streak are the cause of the malformations and the somite alterations secondary to these disturbances. GIROUD and MARTINET noted that the cranial vault is never completely formed in the vitamin A induced anencephaly of mouse embryos. They considered this to be the result of lack of induction of bone formation by the abnormal brain. They also found an open and everted neural tube in the cephalic region of young embryos and conclude, in favor of the classic view, that a primary disturbance in the neural tissue is the cause of the malformation. Their observations, however, were made in embryos more than 24 hours after the administration of the vitamin. MARIN-PADILLA and FERM found that somite necrosis can be detected within 12 hours following the administration of this teratogen to the pregnant animals. Embryos obtained later (more than 24 hours) showed the typical neural tissue malformations but these had, of course, passed beyond the critical stages at which somite necrosis could be detected. Also, somite disturbances causing disorders of segmentation in early embryos and resulting in later skeletal defects of the vertebral column have been described in inherited diseases in the mouse (THEILER; MATTER; GRÜNEBERG).

In conclusion, the study of clinical material (the sphenoid bones of human cranioschisis and craniorhachischisis) together with experimental observations support the concept that cranioschisis is caused by a cephalic disturbance resulting from cellular necrosis of the somites.

Summary

A study of the sphenoid bone of five cases of human cranioschisis and craniorhachischisis is presented. All the sphenoid bones studied are similarly malformed regardless of the severity of the malformations and the extent in the degeneration of the nervous tissue. The most characteristic abnormalities common to all the sphenoid bones studied are: a reduction in the transverse diameter, a prominent rostrum occupying the anterior surface of the bone and an abnormal position of the bone in the base of the skull. The similarity of the abnormalities in all sphenoid bones studied supports the idea of a basic segmental disturbance in the axial cephalic mesoderm which may result from primary alterations of the somites. The cellular necrosis of somites found in experimentally induced cranioschisis support to above contentions.

Untersuchungen über das Keilbein bei der Cranioschisis und Craniorhachischisis des Menschen

Zusammenfassung

Fünf einschlägige, verschieden stark ausgeprägte Fälle wurden untersucht. Alle untersuchten Keilbeine waren in ähnlicher Weise mißgestaltet, und zwar unabhängig von der Schwere der Gesamtmißbildung und des Ausmaßes der Degeneration des Nervengewebes. Die am meisten kennzeichnende Abnormität bei allen untersuchten Keilbeinen bestand in einer Verkleinerung seines Querdurchmessers, Vorragen des Rostrums, welches die Voderfläche des Knochens einnahm, und einer abnormen Stellung des Keilbeins in der Schädelbasis. Die Ähnlichkeit der Abnormität bei allen Keilbeinen stützt die Annahme einer ursprünglichen segmentären Störung des axialen Kopf-Mesoderms, die ihrerseits auf eine primäre Störung des Somiten zurückgeht. Die Nekrose von Somitenzellen, welche bei experimentell hervorgerufenen Cranioschisis zu finden ist, entspricht durchaus dieser Annahme.

References

Augier, M.: Squelette céphalique. Poirier. Traité D'Anatomie Humaine, 4. éd., tome I, p. 627—628. Paris: Masson & Cie. 1931.

Beer, G.R. de: The development of the vertebrate skull, p. 484—485. Oxford: University Press 1937.

Deppe, B.: Beiträge zur Frage der Skelettverhältnisse bei Anencephalie und Craniorhachischisis. Virchows Arch. path. Anat. **293**, 153—164 (1934).

Feller, A., and H. Sternberg: Zur Kenntnis der Fehlbildungen der Wirbelsäule. I. Die Wirbelkörperspalt und ihre formale Genese. Virchows Arch. path. Anat. **272**, 613–640 (1929).

Gallera, T.: Influence de l'atmophère artificiellement modifiée sur le developement embryonnaire du poulet. Acta anat. (Basel) **11**, 549—585 (1951).

Giroud, A., et M. Martinet: Anencéphalie expérimentale chez la souris et comparaisons avec l'anencéphalie chez l'homme. Acta anat. (Basel) **44**, 358—370 (1960).

Grüneberg, H.: The pathology of development. A study of inherited skeletal disorders in animals, p. 146—171. Oxford: Blackwell Sci. Publ. 1963.

Marin-Padilla, M.: (1) Study of the skull in human cranioschisis. Acta anat. (Basel) (in press).

— (2) Study of the vertebral column in human craniorhachischisis. The significance of the notochordal alterations. Acta anat. (Basel) (in press).

—, and V. Ferm: Somite necrosis and developmental malformations induced by vitamin A in the golden hamster. J. Embryol. exp. Morph. **13**, 1—8 (1965).

Mathis, H.: Über 9 Fälle von Kraniorachischisis (spina bifida) mit besonderer Berücksichtigung des axialen Skeletts. Virchows Arch. Path. Anat. **257**, 364—391 (1925).

Matter, H.: Die formale Genese einer vererbten Wirbelsäulenmißbildung am Beispiel der Mutante Crooked-Tail der Maus. Rev. suisse Zool. **64**, 1—38 (1957).

Recklinghausen, F. v.: Untersuchungen über die spina bifida. II. Über die Art und die Entstehung der spina bifida, ihre Beziehung zur Rückenmarks- und Darmspalte. Virchows Arch. path. Anat. **105**, 296—330 (1886).

Sternberg, H.: Über Spaltbildungen des Medullarrohres bei jungen menschlichen Embryonen, ein Beitrag zur Entstehung der Anencephalie und der Rachischisis. Virchows Arch. path. Anat. **272**, 325—373 (1929).

Theiler, K.: Störungen der Ursegmentbildung durch mutierte Gene bei der Hausmaus. Arch. Klaus-Stift. Vererb.-Forsch. **31**, 285—290 (1956).

Weinhold, H.: Untersuchungen über das Wachstum des Schädels unter physiologischen und pathologischen Verhältnissen. I. Teil. Beitr. path. Anat. **70**, 311—341 (1922).

Willis, R.A.: The border of embryology and pathology, 1st ed., p. 147—163. London: Butterworth & Co. 1958.

Miguel Marin Padilla M.D.
Dartmouth Medical School, Department of Pathology
Hanover, New Hampshire (U.S.A.)