Human prenatal craniofacial development related to brain development under normal and pathologic conditions

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A survey is given of current knowledge of the interrelationship between facial, cranial and brain development in humans. First, normal facial, cranial (mandible, maxilla, palatine bone, cranial base, theca cranii, dentition), and brain development are described separately. Then, developmental interrelationships are illustrated under normal and pathologic conditions (cleft lip and palate, holoprosencephaly, anencephaly, amniotic band sequence). New observations are described in detail, and references are given to previously published articles. A close interconnection exists between the development of the face, the craniofacial skeleton, and the brain. This is illustrated by new observations in cleft palate fetuses and new theories about the etiology of holoprosencephaly and tooth agenesis. The survey focuses, moreover, on the importance of the face and the cranial base in endocrine development. Borderlines between face regions and cranial regions with different developmental origin are set up for future elucidation of the etiology behind syndromes involving the craniofacial regions. □ *Anencephaly; holoprosencephaly; neural crest; notochord; pituitary gland*

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Human prenatal craniofacial development cannot—as is customary—be separated from development of the central and peripheral nervous system. At the very earliest stage in prenatal development, about the 15th day, the region that will later become the human head, the prechordal region, is located in front of the anterior end of the notochord. The prechordal area is made up of surface ectoderm, which later becomes the face, and in direct contiguity with this epithelial layer is the neuroectoderm, from which the brain develops (1, 2).

Mesenchyme, which is the basis for cranial development, is not found in the cranial region at this early stage. Mesenchyme does not form until about day 18, when neural crest cells invade the region. The mutual interaction of surface ectoderm, neuroectoderm, and mesenchyme at this early stage is the foundation for craniofacial development (3–9).

In what follows the development of the face, cranium, and nervous system will first be considered individually; then the interrelationship of these tissues will be elucidated under normal and pathologic conditions, focusing especially on osseous and nervous tissue interactions. Attention will primarily be concentrated on a detailed description of new observations, whereas references will be given to previously published results.

Facial development

The prechordal cell layers grow in the anterior and cranial direction from the 15th to the 18th day. The surface ectoderm is smooth and comparable in form to a fingertip, with the neuroectoderm constituting the nail. In the early embryonic head the rostral neuropore is open (Fig. 1). The actual closure occurs bidirectionally, partly from the facial side (the edge of the nail) and partly from the back (the root of the nail) (2) (Fig. 2). After closure the nasal placode, the optic placode, the maxillary process, the mandibular process, and the otic placode appear. This appearance of the facial prominences and gill arches, frontally vaulted and depressed, is connected with the invasion of mesenchyme between the two ectodermal cell layers, caused by the migration of neural crest cells penetrating the layers in a cranial-caudal direction (Fig. 3). The facial morphology gradually changes with the change in nasal and aural morphology (Fig. 4) (6, 9–11).

Cranial development

The onset of development of the craniofacial skeleton takes place roughly in the following chronologic sequence: mandible, maxilla, palatine bone, cranial base/theca cranii, and tooth development.

Mandible

Ossification begins in what will later be the canine region, which at this stage corresponds to the mental foramen region, on the outer side of Meckel's cartilage. Anterior to the canine region the mandible is formed

Fig. 1. The rostral neuropore (RNP) in the early embryonic head, age 25 days. SE = surface ectoderm; NAS = nasal placode.

by enchondral ossification and posteriorly by intermembranous ossification (12). The condylar cartilage forms independently of Meckel's cartilage at the posterior border of the intermembranous part of the mandible (13, 14). Development and growth in the symphysis menti and the mandibular condyles have previously been described in detail (15).

Maxilla and palatine bone

In the maxilla, too, ossification commences in what will later be the canine region, which here corresponds to the region of the infraorbital foramen, from which it proceeds anteriorly and posteriorly. Next, the ossification of the vertical part of the palatine bone commences in relation to the palatine nerve, at the level of the future palate. This is followed by ossification of the border contours of the incisive foramen, first the anterior border and later the posterior one. The ossification of the hard palate spreads gradually from the canine region out into the palate (16–18). The pattern of ossification in relation to the peripheral nervous system has been described earlier (19). Growth in the palate takes place primarily in the median and transverse palatine sutures. The incisive fissure seems to be organized chiefly to make room for the developing incisors (20). The transverse palatine suture in the sagittal plane is so inclined that the sutural growth transports the maxilla downwards and forwards. Fig. 5 presents illustrations of the prenatal palate in the horizontal and sagittal plane. Cephalometric studies have shown that the maxillary edge of the suture grows considerably more than the palatinal edge (21).

Cranial base and theca cranii

When the main structures of the mandible and maxilla are fully developed, ossification of the cranial base and theca cranii begins. Midsagittally, the ossification of the cranial base follows a very definite sequence from the foramen magnum to the region of the nasal bone (22–25). The pituitary gland has developed before the cartilaginous cranial base has formed (26). In the lateral part of the cranial base a clear ossification sequence has been described (27, 28). The growth of the cranial base has also been described in recent years (29, 30).

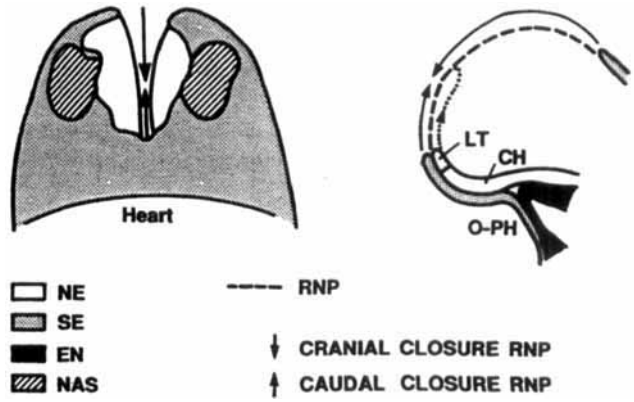

Fig. 2. *Left*: Frontal view of the rostral neuropore (RNP) and the bidirectional closure (indicated by arrows) in the early embryonic head, age 25 days. SE = surface ectoderm; NAS = nasal placode. *Right*: Sagittal section of the specimen (shown on left). LT = terminal lamina; CH = optic chiasm; neuroectoderm; O-PH = oropharyngeal membrane; EN = endoderm. Modified after O'Rahilly & Müller (2), with permission.

The dentition

The dentition starts to develop early in embryonic life, but mineralization of the tooth germs does not start until ossification has occurred in the supporting tissue in which the teeth develop. The maturation of the dentition follows that of the jaw skeleton and also the skeletal maturation of the cranial base. The details have been presented in various articles (31–35).

Brain development

The forebrain, the anterior end of the closed neural tube, develops from the neuroectoderm of the prechordal area. The pituitary gland, which is located posteriorly in the forebrain, develops immediately in front of the anterior end of the notochord (11, 26). The closure of the neural tube starts at the level of the 4th to 5th somites in the cervical region of the embryo and proceeds like a zip-fastener upwards and downwards from this region. At the edges, where the surface ectoderm and neuroectoderm of the bilateral forebrain components meet, neural crest cells are released, clearly arising in groups corresponding to the frontonasal process, the maxillary process, and the mandibular process (3–6). These neural crest cells migrate from their original sites at the edges before closure of the anterior neuropore occurs. Immediately after the closure of the neural tube on the 28th day, hemisphere development commences as two bulges, resembling two half walnut kernels, which increase in size and gradually cover the roof of the brain stem (10, 11).

The olfactory, optic, and otic placodes develop in close connection with the forebrain neuroectoderm (10, 11).

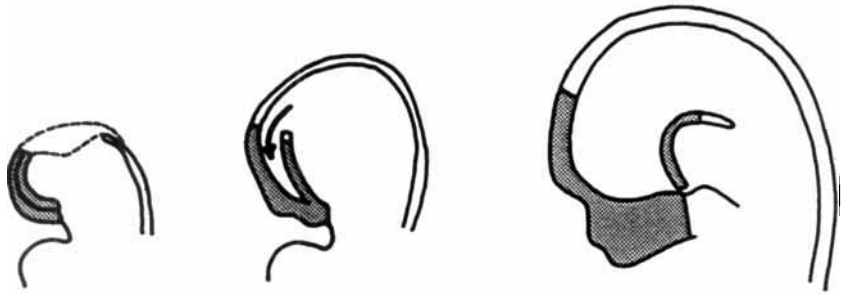

Fig. 3. The originally close connection between surface ectoderm and neuroectoderm (left); mesenchymal invasion close to surface ectoderm and separation of craniofacial and central brain structures due to development of the hemispheres (indicated by arrow in center of figure); and change in the cranial morphology (right).

Interrelationship between facial development, cranial development, and development of the central and peripheral nervous system

Prenatally, a close correlation has been observed between closure of the soft palatal shelves and the ossification pattern in the jaws and cranial base (17, 36). In orthodontics it is customary to relate cranial development and dental development to general skeletal development, assessed from hand roentgenograms. Similar relationships have also been registered prenatally by relating the course of cranial development to skeletal development in the hand and foot (37). Paradoxically, however, the much closer relationship that exists between the cranium and the brain has never been the subject of systematic maturity analysis, either prenatally or postnatally.

In normal prenatal life a close correlation was found between peripheral nerve branches and ossification (19, 38) and between nerve branches and tooth mineralization (31, 32, 34, 35). In the cranial base a close correlation was found between pituitary gland development and development of the cranial base (26). In the cervical spine the corpora of the vertebrae developed in the caudal-cranial direction, thus following the developmental direction of the notochord, whereas the arches developed in the cranial-caudal direction depending on the outgrowth of the peripheral nervous system (39, 40).

An additional way to elucidate this relationship is to describe pathologic conditions in which facial malformations, cranial malformations, and/or nervous tissue malformations occur. Against this background hypotheses will be proposed for developmental relationships and developmental borderlines in the course of prenatal craniofacial development.

The following malformations and disruptions will be covered: cleft lip and palate, holoprosencephaly, anencephaly, and amniotic band sequence involving the theca cranium.

Cleft lip and/or palate

Face. In addition to the cleft of the lip and palate, the eyes are further apart in both prenatal and postnatal life, and the cranium as a whole is shorter and broader (41, 42).

Craniofacial skeleton. In addition to the cleft in the hard palate and/or clefts in the alveolar process, an increased distance is observed between the postnatal vertical parts of the palatine bone (43). In some fetuses malformations were seen in the presphenoidal component of the cranial base (Fig. 6) which have not previously been described. Deficient growth in the cartilage primordium of the

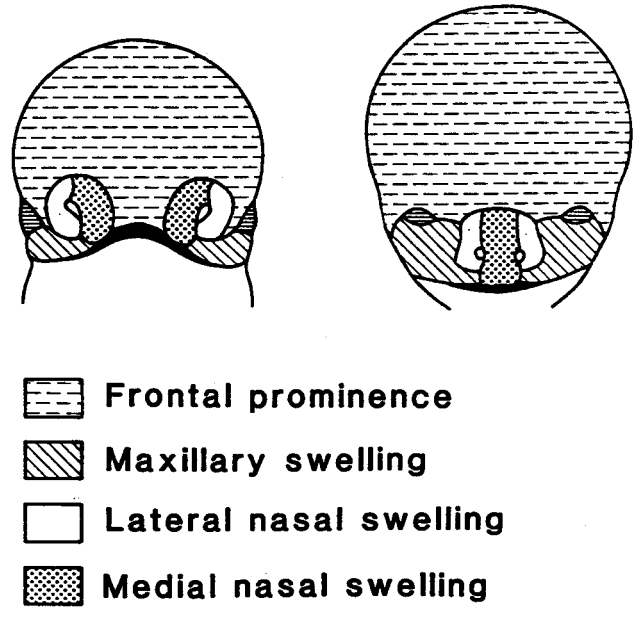

Fig. 4. Facial formation by frontal prominence, maxillary swellings, lateral nasal swellings, and medial nasal swelling in human faces at 6 weeks (left) and 10 weeks (right) of age (46).

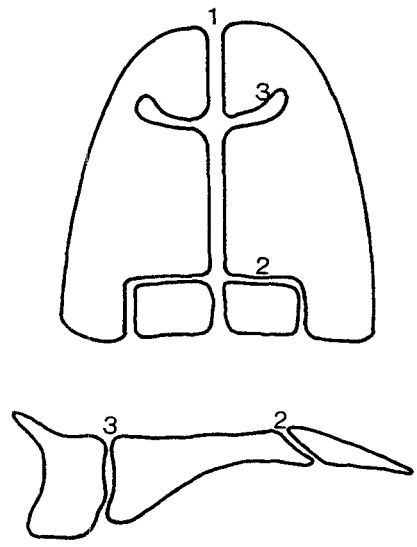

Fig. 5. Upper drawing shows the palatal suture system in the horizontal plane. The midsagittal suture is in the center (1), and the transpalatine suture perpendicular to the midsagittal suture (2). The anterior fissure (3) indicates the incisive fissure in the maxillary bone. Lower drawing shows a parasagittal section of the human fetal palate. The incisive fissure (3) and the transpalatine suture (2).

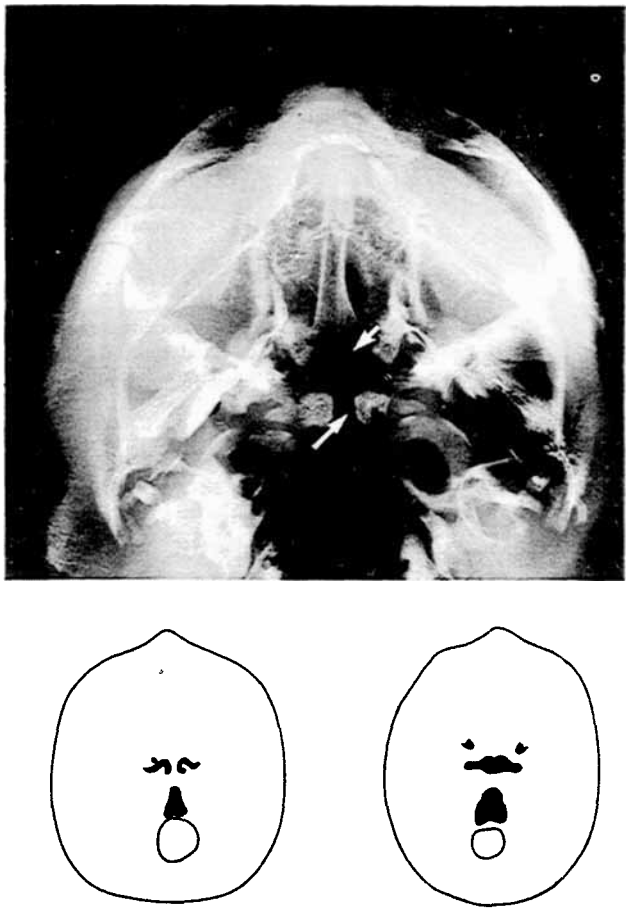

Fig. 6. Radiograph in vertical projection of the anterior part of the cranial base in a 20-week-old human fetus. Short arrow indicates contour of soft palate cleft. Long arrow indicates malformation in the underlying presphenoid and postsphenoid bones, shown in inserted diagrams (right is normal).

cranial base would also affect cranial base shape and growth, as the base in its origin is a continuous plate of cartilage (44).

Nervous system. Studies have seemingly not been undertaken to elucidate the relationship between craniofacial development and development of the central and peripheral nervous systems in fetuses with cleft lip and/or palate.

Holoprosencephaly

In this condition, which is a polytopic field defect anterior to the sella turcica characterized by malformation of the face, craniofacial skeleton, and brain, described earlier (45, 46), the following defects are seen:

Face. Malformations are seen in the midline of the face, in descending order of severity, ranging from anophthalmia and cylopia defects to minor upper lip malformations. It is characteristic that there is always malformation in the labial area and that the facial malformations are very extensive if the upper facial regions are affected.

Craniofacial skeleton. Holoprosencephalic malformations that involve all the bones of the face and those that only involve a few bones have been observed. In the cranial base the presphenoidal component is always malformed. In the facial cranium it is the premaxillary component of the maxilla that is invariably malformed. The following are seen in the nasal cavity: a) multilocular nasal septum, b) short septum, c) cleft palate, d) apparently normal contours of the nasal cavity. The same pattern of descending degrees of malformation in the cranial-caudal direction which is observed in the face is seen in the craniofacial skeleton.

Central nervous system. In holoprosencephaly two forms of brain defect have been described. These are alobar malformation, which is seen in cases of the severest facial malformations, and various degrees of lobar malformation, which are seen in the remaining, milder cases of facial malformation (45). Pharyngeal adenohypophyseal tissue is seen, and normal localization of the neurohypophysis (47). Malformation of cranial base components posterior to the sella turcica is never observed, whereas malformations are always seen anterior to the sella turcica (46).

Anencephaly

In anencephaly the theca cranii has not formed, and

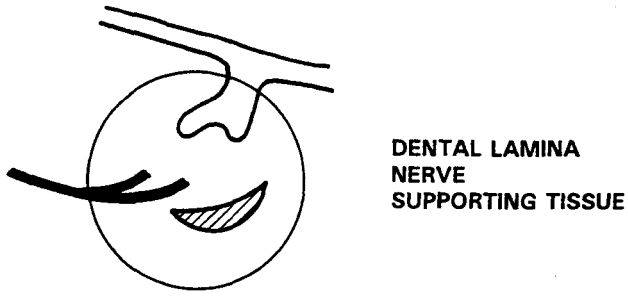

Fig. 7. Three different types of tissue important for tooth formation. Dental lamina (white), nerve tissue (black), and supporting tissue (hatched).

only parts of the brain tissue components occur. The condition is due to insufficient development or function of the notochord. Anencephaly may be accompanied by a greater or lesser degree of rachischisis, either locally along the spine or in direct connection with the anencephalic cranial aperture (48–55).

Face. The anencephalic face has a characteristic appearance, in particular with protruding eyes. In addition, choanal atresia and cleft lip may occur (56).

Craniofacial skeleton. The craniofacial skeleton in the region of the nasal cavity may be of four different types: a) apparently normal, though deformed; b) cleft palate; c) short nasal septum; d) multilocular cartilaginous contours. It is characteristic that behind the seemingly normal, or almost normal, facial contours there may be a severely malformed facial skeleton (56). The cranial base is, compared with normal findings (57), always malformed posterior to the sella turcica region, and sometimes also anterior to it (55). Craniopharyngeal canals are seen in the cranial base (40, 47).

Central nervous system. In anencephaly remnants of cerebral tissue occur. Medulla oblongata and pons are often observed. Neurohypophyseal tissue is not registered, and adenohypophyseal tissue is found, partly cranially and partly pharyngeally (47).

Amniotic band sequence involving the theca cranium

According to the definition of Spranger et al. (58), amniotic band sequence is a disruption. The special kind of disruption, which involves the theca cranii, can be difficult to distinguish from anencephaly, which belongs to the group defined as malformations.

Amniotic band sequences are all different. The face, the craniofacial skeleton, and the central nervous system are involved, depending on the localization of the amniotic band and the stage of development when the amnion band disrupted the cranium (59). The bony tissue serves in these cases as adequate markers in differential diagnostics and in determining the individual prenatal developmental stage at which disruption occurred (60).

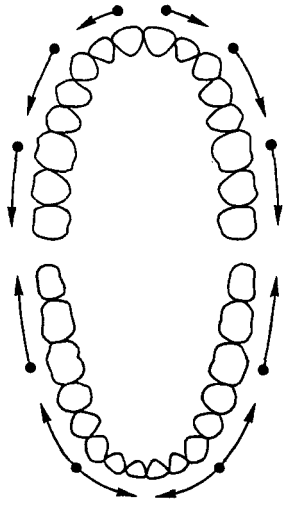

Fig. 8. Upper and lower dental arches. Filled circles indicate prenatal area of nerve foramina (located lingually or buccally) and early ossification sites. Arrows indicate the direction of the nerve branching from the foramina. The arrows also indicate the sequence in which the initial mineralization of the teeth occurs in relation to the foramina.

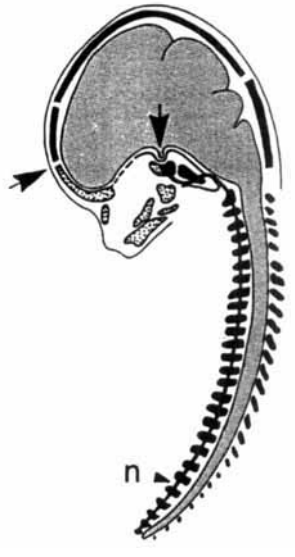

Fig. 9. The central nervous system and the surrounding axial skeleton, consisting of the spine, the basilar part of the occipital bone, the cranial part of the craniofacial skeleton, and the theca bones (40). The original location of the notochord (n) is marked (black). The vertical arrow indicates the sella turcica, and the oblique arrow the presumed site in the frontal bone where the neural tube closure from anterior and posterior direction meets. The craniofacial skeleton between the arrows has developed from neural crest cells, and the remaining skeleton either from para-axial mesoderm, as indicated, or only in part from para-axial mesoderm.

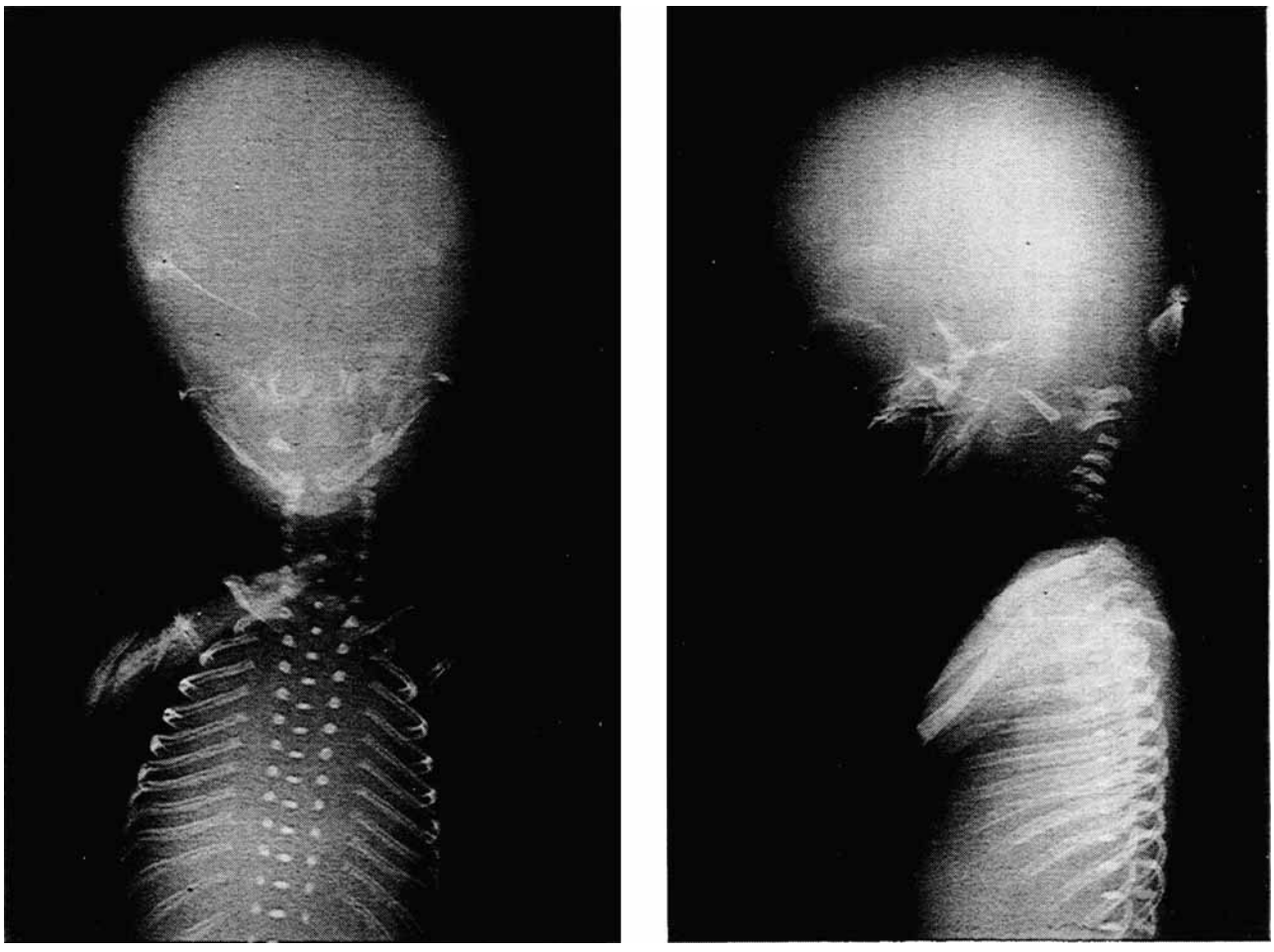

Fig. 10. Radiographic frontal appearance (left) of a human fetus (age 15 weeks) showing actual status of ossification in the cranium, the cervical and thoracic vertebrae, and the ribs. Same fetus in lateral projection (right). Note the advanced ossification of the craniofacial skeleton compared with the ossification stage of the neurocranium.

Conclusions and discussion

The face, the craniofacial skeleton, and the central and peripheral nervous systems are developmentally interconnected. A brief account of the development of the face has been given, followed by a more detailed account of the development of the craniofacial skeleton and, finally, by a brief account of the development of the central nervous system. The interconnection of the courses of development is illustrated by a survey of the pathologic conditions, which shows the following:

The facial development is dependent on the development of the early surface ectoderm in the prechordal area and of the interaction of this epithelial layer with the supporting neuroectoderm. It is suggested that a harmonious proliferation of these two layers and/or separation of the layers at the right time or in the right manner is decisive for the neural crest cells to penetrate into the interepithelial space, forming the ectomesenchyme, from which the craniofacial skeleton is formed. It is proposed that, unless the prosencephalic neural crest cell migration occurs normally, a holoprosencephalic face will develop. Facial development appears to proceed independently of the closure of the anterior neuropore, which occurs after the neural crest cells have already migrated into the face and gill arches (4–6, 8). The cranio-caudal pattern of skeletal severity in holoprosencephaly seemingly reflects the migration path of the neural crest cells and, again, the severity of brain malformation. The etiology of the cleft lip and palate malformation cannot be determined from the studies undertaken hitherto. It is supposed that there are several etiologic factors, one of which may be a diminished migratory tendency of the neural crest cells that are to form the maxillary processes.

The craniofacial skeleton seems to be developmentally closely connected to the development of the central and peripheral nervous system. It may be

severely malformed when the facial contours are almost normal (56). No explanation can be given for this, but one possible hypothesis could be that neural crest cells responsible for skeletal development have their origin on the neuronal part of the crest. It seems logical that the central nervous system and the cranial skeleton are developmentally interdependent, since earlier investigations have shown that there is an initial ossification pattern in the jaw skeleton which closely follows the development of the peripheral nerves (19). This applies both to the localization of the initial ossification and to the sequence in which these ossification sites arise. The nasal and vomeral bones seem to be dependent on the nasal cartilage in their development (61).

The development of the teeth seems, however, to depend partly on surface ectoderm, partly on the innervation of the ectomesenchyme, and partly on the mesoderm that surrounds it (62) (Fig. 7). The most frequently observed tooth agenesis pattern seems to be related to the pattern of innervation (Fig. 8).

The development of the central and peripheral nervous system depends on several factors, important among which is the influence of the notochord on the closure of the neural tube. The development of the pituitary gland seems to be dependent on the surface ectoderm (adenohypophysis), the neuroectoderm (neurohypophysis), and the mesoderm, which form the cranial base.

Ongoing studies of the relationship between the nasal placode and the development of the hypothalamus confirm that the luteinizing hormone-releasing hormone (LHRH) neurons migrate from the area of the nasal placode (63). The development of the face and cranial base is therefore of critical importance for human endocrine functions.

Developmental borderlines

In the face, craniofacial skeleton, and central nervous system there are borderlines between regions with different developmental origins. In the sella turcica there is a borderline posterior to which the developmental origin of the cranial base depends on the notochord, which is not the case anterior to the sella turcica (Fig. 9). Another borderline is seen at the boundary of the lower third of the frontal bone (Fig. 9). This is the presumed site in the frontal bone where the closure of the neural tube from anterior and posterior directions occurs. Below this borderline it is the neural crest cells that are responsible for the craniofacial development. Above this forehead borderline it is, according to Le Lièvre (64) and Siebert et al. (45), the parachordal tissue, which migrates upward with the development of the hemispheres, thus forming the upper theca cranii components. According to Couly et al. (65), however, this upper part of the cranium originates from neural crest cells. When this upper part does not form, as in anencephaly, the face appears with a short frontal bone (46). The anencephalic condition is, according to most reports, due to notochordal insufficiency (66). Other borderlines are the bilateral diagonal lines across the face indicating the position of the early crest ridge of the neural tube (48).

Current studies of skeletal development in fetuses with known genetic defects will, presumably, soon contribute to establishing genetically determined borderlines such as borderlines that have been defined for the expressivity of the Hox genes (67–69). It is expected that such borderlines will contribute to elucidating etiologic aspects of different syndromes.

The craniofacial skeleton is the cranial part of the axial skeleton (Fig. 10). The notochord influences only a minor part of the development of the cranial base, but it affects the whole development of all the spinal corpora. A malformation anywhere along the notochord has been shown to involve malformations in other regions along its course (55). Future accounts of craniofacial development, intended to solve developmental riddles hidden in the syndromology, should therefore comprise an account of the entire axial skeleton.

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