The Cloverleaf Skull Anomaly: An Anatomic and Histologic Study of Two Specimens

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Two neonatal human specimens exhibiting the cloverleaf skull anomaly were studied in detail using gross, radiographic and histologic techniques. Both specimens exhibited premature fusion of the right and left coronal sutures, right and left lambdoidal sutures, and midsagittal sutures. Although the specimens grossly exhibited a similar trilobed appearance of the craniofacial complex, the interrelationship and spatial orientation of their respective articular and skeletal components differed markedly. The development of the cranial base in one specimen appeared normal, while in the other specimen, the synchondroses between the supraoccipital, exoccipital, basioccipital, basisphenoid, and presphenoid bones were prematurely obliterated histologically, resulting in a substantial decrease in the length of the cranial floor. The latter specimen also exhibited micromelic shortening of the limbs with abnormal chondrocyte proliferation and maturation at the epiphyseal growth plates. The alterations in the size and shape of the calvarial bones subsequent to premature sutural synostosis were more severe in the specimen with premature closure of the cranial base synchondroses. The striking differences observed in the anatomic and histologic analysis of the specimens demonstrated that the cloverleaf skull malformation must be etiologically and pathogenetically heterogeneous.

KEY WORDS: Cloverleaf skull, craniosynostoses, neonatal specimens

The cloverleaf skull (trilobed skull, Kleeblattschädel) anomaly was discussed by Holtermüller and Wiedemann in 1960. They presented an affected four and one-half year old child and reviewed 12 earlier cases from the literature. Vrolik reported a case as early as 1849. Many additional cases have appeared in the literature (Weingartner, 1961; Liebaldt, 1964; Comings, 1965; Angle et al., 1967; Moscatelli et al., 1968; Wollin et al., 1968; Feingold et al., 1969; Nawalka and Mangal, 1970; Schuch and Pesch, 1971; Partington et al., 1971; Cohen, 1972; Hall et al., 1972; Bonucci and Nardi, 1972; Feingold et al., 1973; Eaton et al., 1975; and Cohen, 1975). The condition has also been reviewed extensively elsewhere (Cohen, 1975; Gorlin et al., 1976; Cohen, 1976).

On clinical grounds the cloverleaf skull anomaly has been observed to be etiologically heterogeneous and has been reported in association with the aberrant band syndrome

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(Schuch and Pesch, 1971), Apert syndrome (Feingold et al., 1973), one form of campomelic syndrome (Khajavi et al., 1976), Carpenter syndrome (Cohen, 1972, 1975), Crouzon syndrome (Hall et al., 1972), Pfeiffer syndrome (Eaton et al., 1975; Cohen, 1975), and thanatophoric dysplasia (Partington et al., 1971). The condition has also occurred as an isolated anomaly and has been iatrogenically induced (Cohen, 1975).

The purpose of the present study is to examine in detail the craniofacial articulations in two previously unreported specimens with the cloverleaf skull anomaly and to compare these findings with data from a control specimen. The methodology will consist of a combination of gross, radiographic, and histologic techniques.

Materials

CASE I. A 2710 g newborn male with multiple anomalies was born to a normal unwed 23-year-old primigravida. Delivery was spontaneous with a posterior vertex presentation.

On physical examination length was 48 cm (25th percentile for 42 weeks) and OFC was 31.5 cm (<10th percentile for 42 weeks). Craniosynostosis with cloverleaf skull malformation was evident (Figure 1a). Facial anomalies included proptosis, strabismus, hypoplastic eyebrows, low nasal bridge, small upturned nose with rounded nares, and downturned mouth with prominent, convex, upper lip. The palate was narrow and the alveolar ridges prominent. Preaxial polydactyly was evident on the right hand and both 5th fingers were small. There was 10° limitation of extension at the knees and mild metatarsus adductus. Genital anomalies included micropenis, chordee, incompletely bifid scrotum, and small testes. Cyanosis had been evident since birth and subsequently became worse. The child expired on the second day of life. Autopsy findings included polymicrogyria, hypoplastic frontal lobes with agenesis of the olfactory bulbs and tracts, flattened cerebellar hemispheres with herniation into the cervical spinal canal, and hydrocephalus. Agenesis of the cervical thymic lobes was noted and both lungs were bilobed.

CASE II. A 2000 g newborn male with multiple congenital anomalies was the product of a 36 week gestation, the first-born child of normal parents. The father and mother were 24 years and 23 years of age respectively. Following delivery by caesarean section, the neonate expired after a few, very poor respiratory efforts.

At autopsy the head was observed to be markedly enlarged with a cloverleaf-shaped configuration (Figure 1b). The chest was bell-shaped and all four limbs were micromelic (Figure 2a). Generalized subcutaneous edema was evident; laryngeal involvement was so severe that the lumen of the larynx was almost totally obliterated. Intrathoracic petechiae, reminiscent of those found in the sudden infant death syndrome were observed. The adrenal glands were small (1.2g). Hydrocephalus was evident and was probably secondary to caudal displacement of the brain stem. Histologic examination of the femur showed complete disorganization of endochondral bone formation (Figure 2b). Histologic and clinical findings were consistent with thanatophoric dysplasia.

NORMAL CONTROL. A male specimen with essentially normal articular and skeletal development of the craniofacial complex was selected from the human postnatal collection at the University of Washington, Department of Orthodontics, for gross and histologic comparison with Cases I and II. The gestational period was 35 weeks, the crown-rump length was 34 cm, and the crown-heel length was 46 cm. Although the fetus expired within a few hours after birth, the cause of death was not known.

Methods

After death, the specimens (Cases I, II, and control) were prefused and fixed in 10% formalin. The heads were examined grossly, and the brains were removed from both abnormal specimens and dissected. Measurements were made with a Boley gauge and recorded to the nearest millimeter (Table 1). The three cranial fossae (anterior, middle, posterior) in each specimen were then painted with a barium solution, and basilar, lateral, and posteroanterior radiographs were taken. Tracings of these radiographs were made on acetate paper (Figure 3).

The heads were hemisected parasagittally to preserve midline structures for subsequent histologic evaluation. The right half of each

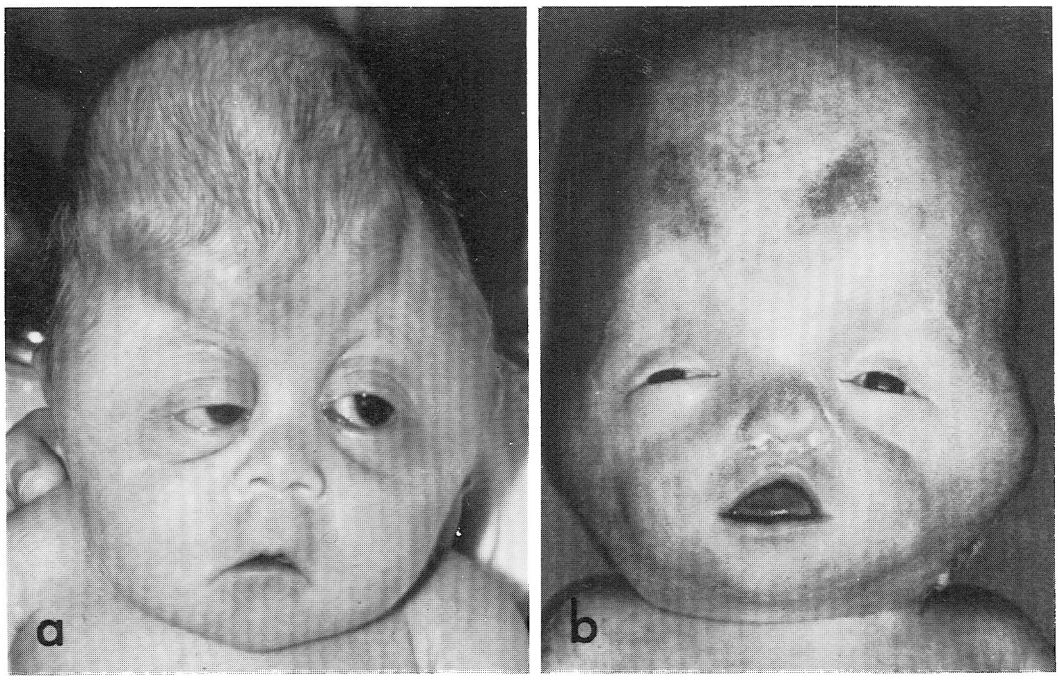

FIGURE 1. Facial photographs of case I (a) and case II (b). Although slight differences exist in the individual craniofacial configuration, both infants exhibit the characteristic trilobed appearance of the cloverleaf skull anomaly.

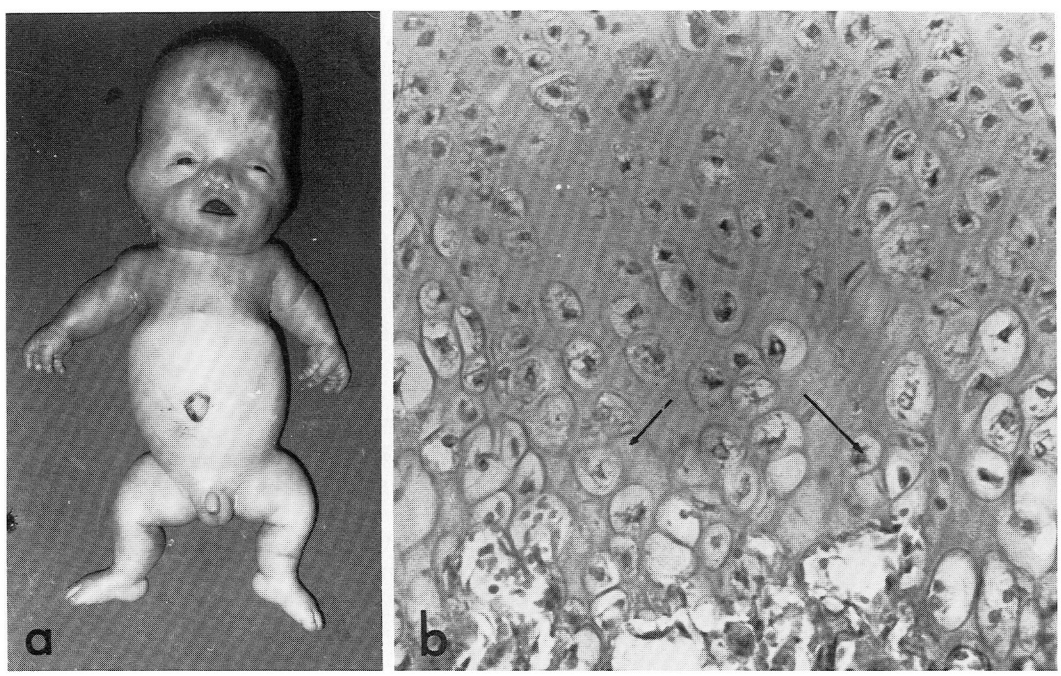

FIGURE 2. (a) Gross photograph of specimen II. In addition to the cloverleaf skull appearance, the chest appeared bell-shaped and all four limbs were micromelic. (b) Photomicrograph of the epiphyseal growth cartilage of the right femur. The cartilaginous plate is characterized by an absence of the normal columnar alignment of cartilage cells in the zone of hypertrophy (arrows). Hematoxylin and eosin. ×75

TABLE 1. Measurements in Millimeters Between Selected External and Internal Skeletal Landmarks

Skeletal Measurements		*Specimen I*	*Specimen II*	*Control*
Foramen magnum	Mediolateral	18	9	12
(diameter)	Posteroanterior	16	9	7
Cribriform plate	Mediolateral	Absent	9	8
(measurements)	Posteranterior		16	16
Interjugular foramen distance*		35	18	24
Intermastoid foramen distance*		45	40	44
Interhypoglossal foramen distance*		20	9	14
Interinternal auditory meatus		36	28	25
Interoptic foramen distance*		11	10	10
Optic chiasma to foramen magnum distance**		43	30	40
Interorbital distance***		47	63	56
Anterior orbital height****		27	23	16

* between the centers of the foramina

** between the most anterior and medial points

*** between the most lateral points on the orbital rim

**** greatest vertical distance between the supraorbital and infraorbital rims

head was impregnated with a 0.5% aqueous silver nitrate solution (Hodges, 1953) and radiographed. The left half of each head was stained with alizarin red S, cleared, and examined grossly. The radiographs and alizarin preparations were compared and analyzed for all recognizable areas of abnormal articular or skeletal development. Tissue blocks containing anomalous areas in specimens I and II were removed from the right half of the heads, stained with hematoxylin and eosin, and examined histologically (Molnar, 1974, 1975a, 1975b, 1975c, 1976). Corresponding blocks were removed from the control specimen and stained in a similar manner for comparison. This sequence and combination of techniques provided a variety of data for analyzing the cloverleaf skull anomaly and suggesting how it may have developed.

Findings

Specimen I

Gross Examination. The anterior cranial fossa was hypoplastic with the absence of a distinct cribriform plate and crista galli. The orbital prominences of the frontal bone were also absent. The middle cranial fossa appeared significantly larger than normal and ballooned laterally and anteriorly (Figure 3), with the petrous crest of the temporal bone directed medially from its proximal end rather than anteromedially. The posterior cranial fossa was shallow and wide. The increased distances between right and left jugular formina, mastoid foramina, hypoglossal canals, and internal auditory meati reflect the degree of lateral expansion of the posterior cranial fossa (Table 1). There were numerous depressions on the internal surface of the calvaria which corresponded well with the previously mentioned microgyri of the cerebral cortex.

Radiographic and Alizarin Examination. All of the cranial bones and several facial bones exhibited compenstory alterations in size, shape, and spatial orientation (Figure 4). The cranial sutural articulations were abnormal in orientation and length and gave radiographic evidence of localized premature synostosis (Figures 4 and 5). In the control specimen, all cranial sutures were patent, except the metopic suture.

In the abnormal specimen, the metopic (interfrontal) suture was fused inferiorly and patent superiorly (Figure 5). The midsagittal suture appeared fused over its entire length. The inferior two-thirds of the coronal (frontoparietal) sutures was fused. The lambdoidal (occipitoparietal) sutures were oriented vertically rather than posterovertically and the superior one-fourth was fused. The middle one-fourth of the left squamous suture appeared fused, but the right squamous suture was entirely patent. The facial sutures did not appear significantly abnormal.

The synchondroses comprising the floor of the middle and posterior cranial fossae ap-

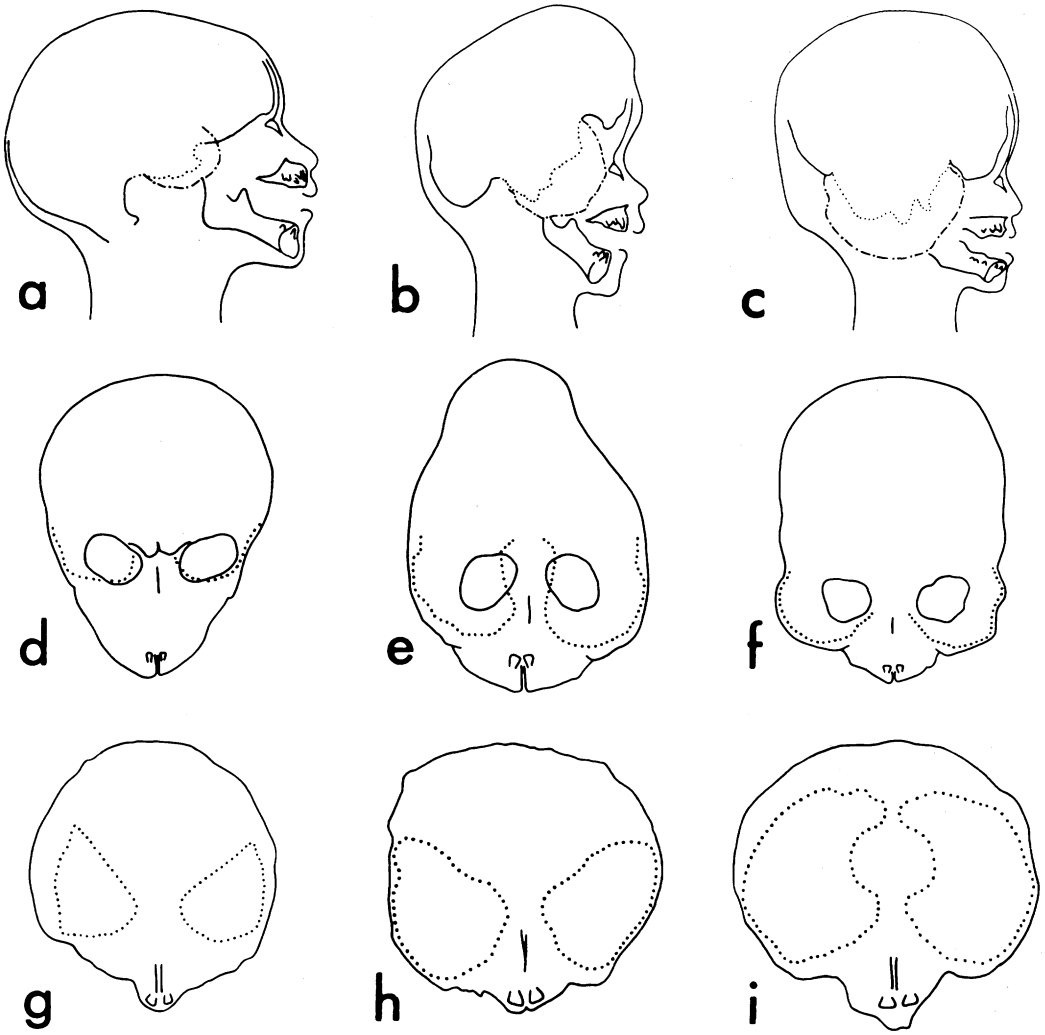

FIGURE 3. Tracing of the relative size and extention of the middle cranial fossa (dotted line) from the radiographs of the control (first column) and specimens I (second column) and II (third column). Lateral view—a, b, c. Posteroanterior view—d, e, f. Basilar view —g, h, i. The middle cranial fossae are greatly enlarged in the pathologic specimens. In specimen I it was located more anteroinferiorly and in specimen II more posteroinferiorly compared to the control. Abbreviations: F, frontal bone; P, parietal bone; O, occipital bone; T, temporal bone, Z, zygomatic bone; S, sphenoid bone; M, maxilla; Mn, mandible.

peared patent, but the basioccipital and exoccipital bones were larger than normal (Figure 5). The radiographs also showed abnormalities in the skeletal trabecular pattern. The frontal, right and left parietal, and occipital bones exhibited numerous areas of cortical thinning which correspond grossly to the previously described gyral depressions.

Histologic Examination. The affected sutures exhibited four distinct zones of abnormal alteration listed in sequence from the point of fusion towards the patent part of the suture: (1) a zone of complete bony union; (2) a zone of partial bony union: (3) a zone of impending bony union; (4) a zone of minimal alteration (Figure 6). All affected sutures exhibited identical cellular, fibrous, and skeletal alterations within these zones.

The zone of complete or total bony union was generally located near the center of the fused portion of a suture. This zone was characterized by a complete obliteration of the

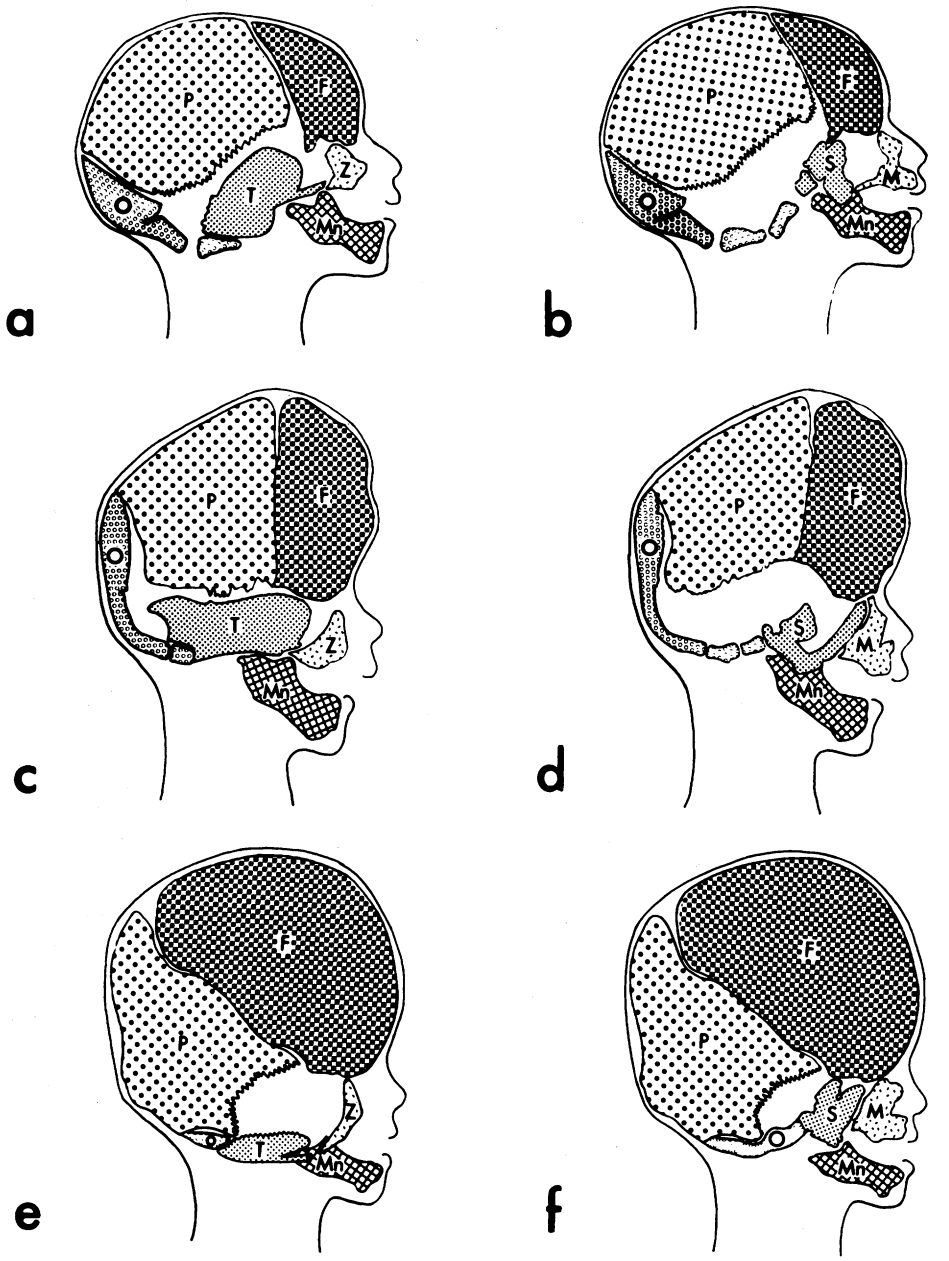

FIGURE 4. Tracing of lateral head radiographs of the control (a, b), specimen I (c, d) and specimen II (e,f) illustrating the relative size and spatial relationships of the cranial and facial bones. It is evident that premature articular synostosis produces secondary deformative alterations in all cranial and facial bones. The differences between the size, shape and orientation of the bones in specimens I and II is dependent upon the number of prematurely fused sutural and cartilaginous articulations. Abbreviations: F, frontal bone; P, parietal bone; O, occipital bone; T, temporal bone; Z, zygomatic bone; S, sphenoid bone; M, maxilla; Mn, mandible; 1, coronal suture; 2, midsphenoidal synchondrosis; 3, sphenooccipital synchondrosis; 4, interoccipital (exoccipital-basioccipital) synchondrosis; 5, interoccipital (exoccipital-supraoccipital) synchondrosis; 6, lambdoidal suture; 7, midsagittal suture; 8, squamous suture; 9, metopic suture.

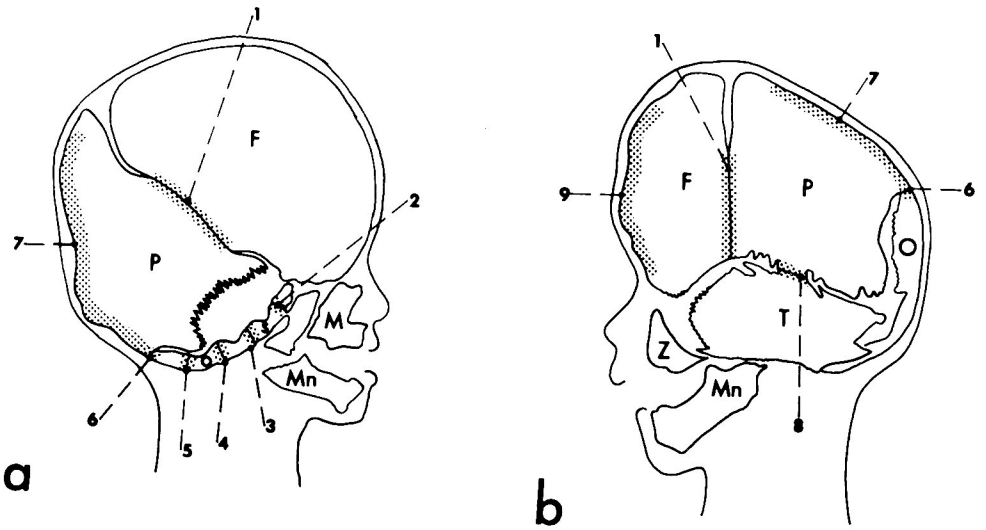

FIGURE 5. Tracings of lateral head radiographs of specimen I (b) and specimen II (a), illustrating the areas of premature craniofacial articular synostosis (stippled portion).

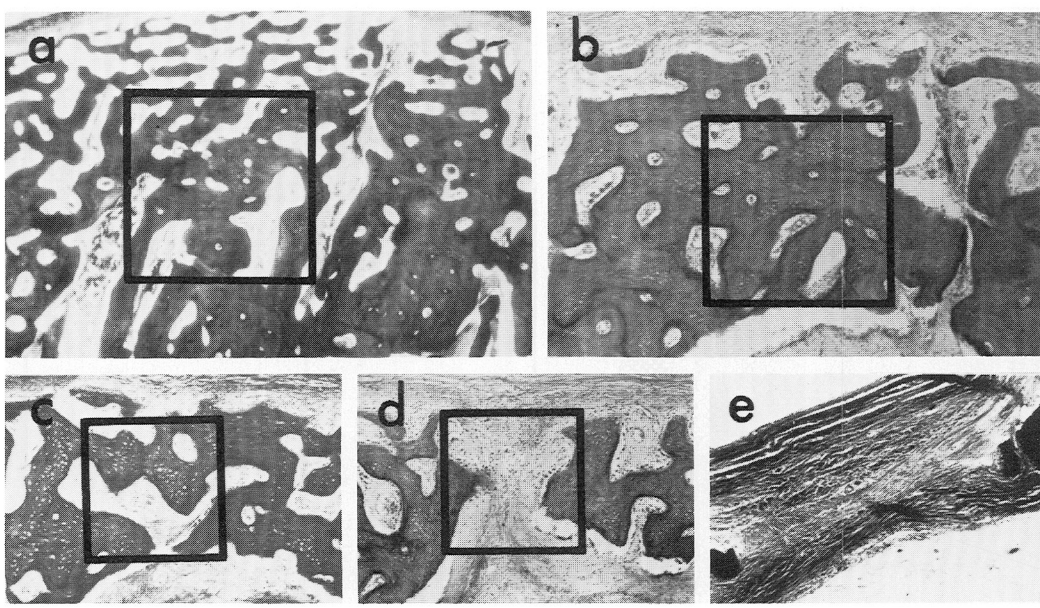

FIGURE 6. Photomicrographs of serial histologic sections of the prematurely synostosed coronal suture from specimen I illustrating the four distinct zones of abnormal alteration: a,b—zone of complete bony union ×16; c—zone of minimal alteration ×8; d—zone of impending bony union ×8; e—zone of minimal alteration ×8. The inset boxed in a,b,c and d identify the area previously occupied by the sutural ligament. Verhoeff's stain.

sutural space by nonlamellar bone (Figure 6a). The zone of partial bony union was characterized by varying degrees of initial fusion of nonlamellar bone across the sutural space, with portions of the sutural ligament still present (Figure 6 b, c). In most of the affected cranial sutures, the initial point of fusion occurred at the ectocranial surface and then proceeded endocranially. The zone of impending bony union was predominantly characterized by marked alterations in the ossifying bony margins of the sutural joint (Figure 6d). The abnormal changes in the zone of minimal alteration became progressively less

apparent in sections further from the zone of impending bony union (Figure 6e). Even in the most remote section, however, alterations were detectable which indicated that premature synostosis had occurred at some point within that particular suture. The most apparent radiographic alteration was a lack of spicules at the sutural bony margins (Figure 7).

The synchondroses of the middle and posterior cranial fossae were removed and examined histologically. Although they appeared slightly narrower than normal, no microscopic abnormalities were detected in the chondrification and ossification of the cartilage.

Specimen II

Gross Examination. The anterior cranial fossa was smaller and shallower than normal. The cribriform plate was present but appeared triangular in shape with the apex located anteriorly. The crista galli was more pronounced. The orbital prominences of the frontal bone were absent. The middle cranial fossa was extremely enlarged, extending laterally and posteriorly and completely surrounding the greatly reduced posterior cranial fossa (Figure 3). The petrous crests of both temporal bones was distorted into arcs which enclosed the underdeveloped occipital bone. The increased distances between right and left jugular foramina, mastoid foramina, and hypoglossal canals reflect this reduction (Table 1). The distance from the optic chiasma to the anteriormost portion of the foramen magnum was shorter than normal, indicating a reduction in the length of the clivus (Table 1). In addition, the foramen magnum was also reduced in size (Table 1).

Radiographic and Alizarin Examination. All of the cranial bones exhibited compensatory alterations in size, shape, and spatial orientation (Figure 4). The length of the body of the mandible was unaffected, while the ramus appeared shorter and the gonial angle more obtuse. The maxillae, palatine, and nasal bones were larger in size but their spatial orientation appeared unaffected.

The sutural articulations were abnormal in length, width, and orientation, and gave radiographic evidence of localized premature synostosis (Figures 4, 5). The metopic suture was significantly longer than normal, but was patent throughout its length. The anterior fontanelle was larger and located much more posteriorly. The length of the midsagittal suture was unaffected: it was however, oriented in a vertical plane rather than an arc, due to the posterior orientation of the parietal bones. In addition, the midsagittal suture was completely fused over its entire length. The pos-

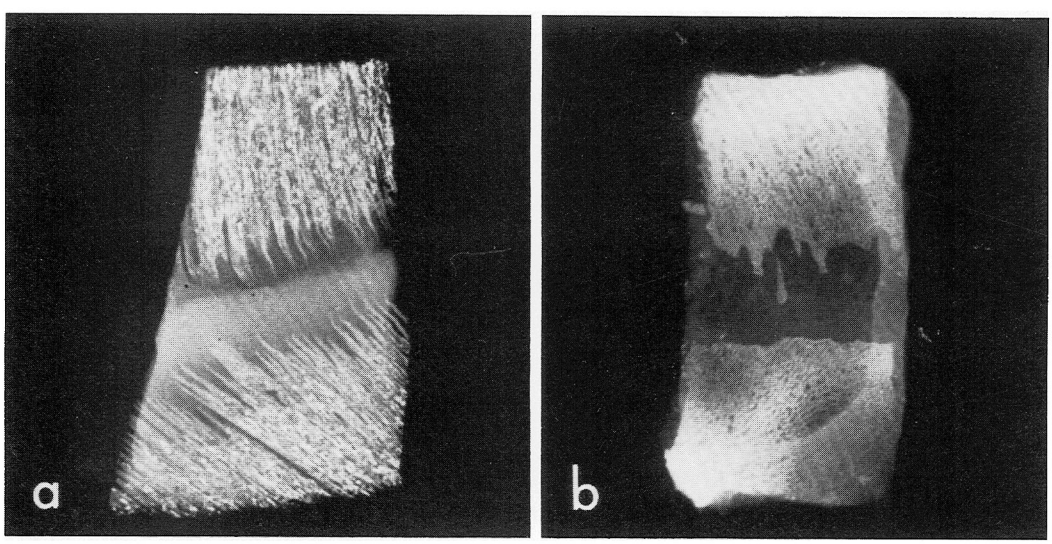

FIGURE 7. Radiographs of tissue blocks containing the coronal sutures from the control (a) and specimen I (b). Note the differences in orientation of the bone trabeculae, and the presence (a) and absence (b) of a "saw-toothed" bony margin in the control and specimen I, respectively. ×4.5.

terior fontanelle was not visible. The inferior half of the coronal suture was fused. The squamous sutures were significantly shorter, but appeared completely patent bilaterally. All facial sutures were patent under radiographic and alizarin examination.

All of the synchondroses comprising the floor of the middle and posterior cranial fossae appeared fused radiographically (Figure 5) and the size and orientation of their corresponding skeletal components were abnormally altered (Figure 4). The size of the basioccipital, exoccipital, and supraoccipital parts of the occipital bone were smaller than normal. The radiographs also showed localized abnormalities in the skeletal trabecular pattern. The right and left frontal and parietal bones exhibited areas of cortical thinning adjacent to the prematurely fused portion of the coronal sutures.

Histologic Examination. Histologic examination confirmed the radiographic interpretation of premature sutural synostosis. Microscopic alterations in the skeletal and fibrous components of these sutures were identical to those previously documented for speciment I (Figure 6).

The synchondroses normally present between the presphenoid, basisphenoid, basioccipital, exoccipital, and supraoccipital components of the skeletal floor at this stage of development were totally absent. The cranial base was completely united as one bone. Other areas were also examined for possible defects in cartilage development. Under microscopic examination, the metaphyseal region of the right femur was characterized by an absence of the normal columnar alignment of cartilage cells at the epiphyseal plate (Figure 2b). The cartilage at the head of the left mandibular condyle, however, appeared unaffected.

Discussion

Although both specimens in the present investigation grossly exhibit a cloverleaf or trilobed appearance of the craniofacial complex, the interrelationship and spatial orientation of their respective articular and skeletal components differ markedly. Of primary significance is the difference in the development of the cranial base between the two specimens. In the first specimen, the cartilaginous synchondroses appeared normal, while in the second specimen they appeared prematurely obliterated, resulting in a substantial decrease in the length of the cranial floor. In addition, the latter specimen exhibits micromelic shortening of the limbs with abnormal chondrocyte proliferation and maturation at their respective epiphyseal growth plates. These characteristic anomalies agree with those reported by Bonucci and Nardi (1972) on a similar specimen with thanatophoric dysplasia. These researchers believe that the development of the cloverleaf skull anomaly is dependent upon a chondrodystrophic condition involving the synchondroses of the cranial base with or without concomitant effects in the epiphyseal growth cartilage of the limbs, ribs, or vertebrae. Specimen I, however, has normal histologic and morphologic cranial base development, so that the cloverleaf appearance was the result of neural expansion in the presence of a particular combination of prematurely fused cranial sutures. Furthermore, previous studies of thanatophoric dysplasia (Giedion, 1968; Langer et al., 1969; Kaufman, 1970; Keats et al., 1970) demonstrated foreshortened cranial base development without premature sutural synostosis and therefore without the characteristic cloverleaf anomaly. It appears that the cloverleaf anomaly may occur as a craniofacial characteristic in thanatophoric dwarfism, but the trilobed configuration is probably not dependent upon a chondrodystrophic abnormality in the cranial base. Rather, it is produced through the restricting influence of a particular pattern of prematurely synostosed cranial sutures on the normal expansion of the brain.

In the present study, both specimens exhibited premature fusion of the coronal, lambdoidal, and midsagittal sutures. This particular pattern of craniosynostosis is in agreement with other investigators (Feingold et al., 1969; Bonucci and Nardi, 1972; Partington et al., 1971; and Angle et al., 1967) who have studied the cloverleaf skull anomaly. The resultant trilobed calvaria is therefore produced by the brain expanding laterally through the patent temporoparietal sutures and superiorly through a portion of the partially patent interfrontal suture and the anterior fontanelle. Cohen's literature reviews (1975; 1976; 1978), noted there was great

variability in the severity of the malformation and that different sutures were involved. Synostosis involved with coronal, lambdoidal, and metopic sutures might show bulging of the cerebrum through an open sagittal suture or through open squamosal sutures. Synostosis of the sagittal and squamosal sutures with cerebral eventration through a widely patent anterior fontanelle was also observed. Trilobular skulls occurred with complete synostosis of all the cranial sutures. Finally, some instances are known in which the sutures were widely patent with no evidence of craniosynostosis at birth.

The present study has demonstrated alterations in the size and shape of the calvarial bones subsequent to premature sutural synostosis. In addition, it appeared that the alterations were much more severe in the specimen with premature closure of the cranial base synchondroses. This finding agrees with those of Partington, et al., (1971) and Bonucci and Nardi (1972), who reported a more posterior and vertical position of the parietal bones, a concomitant increase in size of the frontal bone, and a dramatic reduction in the size of the occipital bone compared to a normal control specimen. Since the majority of the occipital bone (except for the supraoccipital component) is preformed in cartilage, it is dependent upon the patency of the interoccipital synchondroses for normal increases in size during prenatal craniofacial growth and development. In thanatophoric dwarfism, however, the interoccipital synchondroses fuse prematurely, therefore restricting the development in size of the occipital bone, the posterior cranial fossa, and subsequently inducing compensatory alterations in the size, shape, and orientation of the remaining craniofacial skeletal and articular components.

It has been estimated that approximately 40% (N = 51) of all cloverleaf skull malformation cases represent thanatophoric dysplasia and about 20% represent apparent Pfeiffer syndrome (Hodach et al., 1975). The word "apparent" may be appropriate in both instances. All cases of the Pfeiffer syndrome with the cloverleaf skull anomaly have been sporadic. The anomaly has never been reported in a family affected with classic Pfeiffer syndrome, suggesting the possibility of heterogeneity. All instances of thanatophoric dysplasia, except one, have been sporadic to date (Gorlin et al., 1976). The cloverleaf skull anomaly has been observed in sibs affected with thanatophoric dysplasia (Partington et al., 1971). However, no instance of thanatophoric dysplasia with the cloverleaf skull anomaly has ever been observed in a family in which a sib has thanatophoric dysplasia without the cloverleaf skull anomaly, also suggesting the possibility of heterogeneity. Horton et al., (1979) found identical, poorly organized fibrovascular material scattered along growth plates in thanatophoric dysplasia with and without the cloverleaf skull anomaly. The only difference between the two conditions was quantitative suggesting that the same pathogenetic process was operative to different degrees. Horton et al., (1979) suggested that such findings could indicate two distinct disorders causing the same pathogenetic process to different degrees, or to quantitative variability within a single disorder. They favored the latter interpretations.

In contrast to the situation in Pfeiffer syndrome and thanatophoric dysplasia, the cloverleaf skull anomaly has been observed in a family affected with classic Crouzon syndrome (Shiller, 1959). The great variability of other malformations reported in association with the cloverleaf skull anomaly (Cohen, 1975, 1976) suggested that several syndromes of unknown genesis in this group may become further delineated in the future.

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