Prenatal Mandibulofacial Dysostosis (Treacher Collins Syndrome)

ROLF G. BEHRENTS, D.D.S., M.S.
JAMES A. McNAMARA, D.D.S., Ph.D.
JAMES K. AVERY, D.D.S., Ph.D.
Ann Arbor, Michigan 48109

The clinical, radiographic, and histologic aspects of *Mandibulofacial Dysostosis (Treacher Collins Syndrome)* – MFD – are described as observed in a *human fetus* of approximately 15 weeks gestation age. Findings in the present study do not differ significantly from those previously reported, as the abnormal fetus exhibited the peculiar ocular, otic, and mandibular defects common in descriptions of postnatal survivors. Although exhibiting the major signs and symptoms of MFD even at this early developmental stage, previously unreported relationships dealing with the ossification of the mandible and salivary gland hyperplasia are noted. Contrary to expectation, vascularization appears excessive. The pathogenesis of the events leading to the deformities of the first and second branchial arches is extrapolated to seven weeks *in utero*.

Introduction

Numerous investigators have documented and described a syndrome of the head and face which affects the eyes, ears and mandible, under various titles: Treacher Collins Syndrome, Syndrome of Franceschetti, and Mandibulofacial Dysostosis, among others. Description, however, has been limited to observations of living individuals and of autopsy material obtained from postnatal deaths. The purpose of this report is to describe the malformations of the craniofacial complex in mandibulofacial dysostosis (MFD) in a fetus (15 weeks–130 mm. CRL) as revealed by visual, radiographic, and histological observation. This report, therefore, will deal with the syndrome (MFD) at a time of life immediately after the supposed inception of the pathogenic changes which characterize the present syndrome.

Review of the literature

Several hundred cases of MFD have been described in the literature from various geographic locations and racial groups and have been reviewed by Franceschetti and Klein (1949), Axellson *et al.* (1963), Rogers

---

Dr. Behrents is affiliated with the Center for Human Growth and Development, The University of Michigan. Dr. McNamara is affiliated with the Department of Anatomy and Center for Human Growth and Development, The University of Michigan and Dr. Avery is affiliated with the School of Dentistry and Dental Research Institute, The University of Michigan.

This research was supported in part by United States Public Health Service Grants HD-02272, DE-43120 and DE-00193.

(1964) and Roberts, Pruzansky and Aduss (1975). Although observations have each emphasized certain regional aspects of the syndrome, as the result of the various individual descriptions of the signs and symptoms of MFD, a constancy of manifestation has emerged which describes the present syndrome. These signs, as well as the characteristics noted in the present case, are given in Table 1. It must be noted that, while the general similarity in appearance of the affected patients is very striking and consistent, the number and extent of the deformities vary considerably, and thus atypical, incomplete, and unilateral forms have been described, using a variety of nomenclature and diagnostic standards. As a result, the incidence of the syndrome, while not exceedingly rare, cannot be determined with any degree of accuracy. In this same regard diagnosis must be delineated on the basis of a certain number of the most frequently occurring characteristics (Table 1) such as reported by Axellson *et al.* (1963). The approximate age of the development of the structures involved is also given in Table 1, based on the reports of O'Rahilly and Meyer (1956), Patten (1961), Hamilton, Boyd and Mossman (1962), Patten (1968), Langman (1969) and O'Rahilly and Gardner (1973).

Etiology. Attempts have been made to explain the various defects noted with MFD on the basis of a multitude of factors. Poor maternal nutrition, coalescence of amnion strings, x-radiation, pressure, embryo position, vitamin deficiency, variations of temperature, various medicines, diphtheria, diabetes, rubella, measles, toxoplasmosis, atempted abortion, influenza, uterine hemorrhage, tumors, nervous shock, socioeconomic conditions, marital difficulties, and maternal age have all been implicated (McEnery and Brenneman, 1937; Briggs, 1952; Granrud, 1953; Herberts, 1962; Poswillo, 1975). Most emphasis, however, is placed on the hereditary nature of this syndrome (Walker, 1961). In about one-half of the reported cases, there appear to be definite or suggestive heritability trends in familial incidence (Stovin, Lyon and Clemmens, 1960; Rogers, 1964), although apparent spontaneous cases have been reported (Szlazak, 1953; Campbell, 1954; McKenzie and Craig, 1955).

While there can be no real doubt concerning the hereditary nature of this syndrome, (Walker, 1961), considerable disagreement exists regarding the nature of the genetic transmission. Franceschetti and Klein (1949) believe that the defect is caused by an autosomal dominant gene with 100% penetrance and increased risk in progeny of an affected female and decreased risk in the progeny of an affected male. Szlazak (1953) theorized that MFD is transmitted through the female line (sex-linked). Rogers (1964) feels that the anomaly is transmitted by an "irregular dominant gene" that has a variable method by which it is expressed. He states that incomplete forms of the anomaly are an example of weak penetrance; that atypical anomalies involving structures other than the face are an example of the pleiotropic expression of the gene; and that greater incidence of prenatal or postnatal deaths in succeeding affected generations is an example of the increasing lethal effect of the gene.

TABLE 1. Common characteristics of patients diagnosed as having Mandibulofacial Dysostosis and approximate age of development of the structures involved. Key for present case (fetus EH 821): (+), symptoms present; (−), symptoms absent; (*), impossible to determine due to later development or difficulties in diagnosis.

diagnostic features of MFD	*frequency*	*fetus EH 821*	*approximate age of development*
Clinical			
Cranium			
flat parieto-occipital bone	infrequent	*	8 weeks
Midface			
antimongoloid palpebral fissures	obligatory	+	6–8 weeks
colobomas of the lower eyelid	obligatory	+	7–9 weeks
eyelash (or follicle) malformations	obligatory	+	10 weeks
malar defects	obligatory	+	7–8 weeks
atresia of the lacrimal puncta	frequent	*	6 weeks
macrostomia	frequent	*	4 weeks
auricular defects	frequent	+	5–6 weeks
external auditory canal defects	frequent	+	7 weeks
pre-auricular hair elongation	frequent	*	4 months
high arched palate	frequent	+	6–10 weeks
nasal deformity	frequent	+	6–7 weeks
pre-auricular fistulae	frequent	−	6–8 weeks
malocclusion	frequent	*	after birth
colobomas of the upper eyelid	infrequent	−	7–9 weeks
absence of Meibomian glands	infrequent	*	10 weeks
hypertelorism	infrequent	−	6–10 weeks
cleft palate	infrequent	−	6–10 weeks
epiglottis underdevelopment	infrequent	−	6 weeks
parotid gland absence	infrequent	[1]	6 weeks
Mandible			
mandibular defects	obligatory	+	6 weeks
micrognathia	obligatory	+	6 weeks
open bite	frequent	*	after birth
Other			
"fish-like" facial appearance	obligatory	+	?
deafness	frequent	*	?
skeletal defects	frequent	−	?
mental retardation	infrequent	*	?
Radiographic			
Cranium			
accentuated digital markings	frequent	+	7–8 weeks
mastoids small and hypopneumatized	frequent	*	2 months
ossicle defects	frequent	+	6–7 weeks
straight nasofrontal angle	infrequent	+	3 months
malformations of the styloid process	infrequent	*	8–9 weeks
sella turcica defects	infrequent	+	8–9 weeks
sphenoid sinus small	infrequent	*	after birth
persistent frontal suture	infrequent	*	after birth
zygomaticotemporal bones deficient	infrequent	+	7–8 weeks
frontal sinus deficient	infrequent	*	4–5 months
cranial base acuteness	infrequent	+	8–9 weeks
Midface			
zygomatic arch deficient	obligatory	+	7–8 weeks
maxilla hypoplastic	frequent	+	6–7 weeks

[1] The parotid, submandibular and sublingual glands were hyperplastic.

TABLE 1—*Continued*

diagnostic features of MFD	*frequency*	*fetus EH 821*	*approximate age of development*
maxillary sinus deficient	frequent	*	4–5 months
palatine bones deficient	infrequent	+	8 weeks
choanal atresia	infrequent	*	6 weeks
inner ear abnormality	infrequent	−	6–7 weeks
cleft palate	infrequent	−	6–10 weeks
Mandible			
mandible hypoplastic	obligatory	+	6–7 weeks
ramus short	frequent	+	6–7 weeks
body short	frequent	+	6–7 weeks
obtuse gonial angle	frequent	+	6–7 weeks

Chromosome analysis performed on three cases of the incomplete form of MFD revealed no abnormalities (Moss, Saphir and Gottlieb, 1964; Siebner, 1963). Further study is needed to determine the karyotype status of the complete form. However, it is more likely that MFD is associated with a gene defect than with a numerical or gross structural abnormality of the chromosomes.

PATHOGENESIS. The exact sequence of embryological events which together give rise to this group of deformities is obscure. Normal development of the orofacial region in this case depends upon the amount of mesoderm of the first and second branchial arches and the extent and direction of its migration. In a malformation syndrome such as MFD, it is recognized that an important factor affecting the scope of the malformation is the stage of fetal development at the time of injury. It has been theorized that localized groups of cells which are in the most active stage of development are the most vulnerable, which accounts for the very limited regional damage the embryo may sustain. These cells are highly differentiated and cannot be replaced. The damage is, therefore, irrevocable. The organ involved is permanently affected (Granrud, 1953). This could be the case in MFD. Here there appears to be a genetically controlled retardation of growth in the ontogenetic development of the mesoderm in the mandibular arch and its contiguous tissues.

It is generally concluded that defects generated in MFD are the result of defective genetic expression which results in a retardation or failure of differentiation of adjacent tissues in approximately the second month of pregnancy. Franceschetti and Klein (1949) and Briggs (1952) believe that the conditions observed are the result of genetically controlled, defective ossification of the bones of the face derived from visceral mesoderm, which points to the primary lesion occurring about the seventh week of fetal life. It should be noted that a *generalized* ossification defect at that time would probably affect the clavicle and maxilla to equal degrees, which is contrary to reported findings, thus substantiating the regional nature of this malformation syndrome.

Stark and Saunders (1962) feel that the deformities noted are due to a deficiency of mesoderm in the branchial arches—the result of a severe teratologic factor occurring over a long period of time and involving the mesoderm of many separate but adjacent areas.

Mann (1943) states that the syndrome in her case was due to a retardation or failure of differentiation of the maxillary visceral mesoderm at or after the 50 mm. stage (12 weeks). She bases her conclusions mainly on the observed deafness and malformations of the middle ear, the differentiation of which takes place at or before the end of the second month *in utero*. She also argues that the position of the eyes is normal (as are the upper eyelids, upper orbital margins, sclera, and extrinsic ocular muscles), showing that the upward growth of the visceral wedge of mesoderm in the temporal region was normal until the third month. Additionally, an arrest in growth towards the second month is compatible with the presence of normally shaped teeth in the maxilla since the formation of primary dental lamina for these teeth first appears in the sixth week. Eyelash deficiency is expected since the eyelashes and Meibomian glands of the lower lid begin to appear at the 50–60 mm. stage.

In a histopathological study of the temporal bones of a child who died eleven days *post partum*, Sando, Hemenway and Morgan (1968) place the arrest of development between the sixth to the eighth week. They base their conclusions on the developmental course of the facial nerve in relation to the otic structures and the development of the auricle.

Harrison (1951), in describing individual case reports, believes that defects take place over a period of development (in their cases between 30 and 50 mm.), and thus, together with a "concentration effect," temporally determine the extent and number of deformities.

Rogers (1964) points out that the complete form of MFD involves both the first and second visceral arches. He bases his observation on complete involvement of the external ear and stapes, both of which are derived mainly from the second branchial arch. He also speculates that the onset of the condition could occur much earlier than the estimate given by Mann (1943), perhaps as early as the fourth week.

In contrast to theories implicating disturbances primarily in mesoderm, McKenzie (1958) and McKenzie and Craig (1955) hypothesize that the absence or hypoplasia of the stapedial artery might be the cause of damage to the structures of the first visceral arch. This deficiency in blood supply leading to focal ischemic necrosis would occur during the third to the fifth week, at a time when the stapedial artery makes its full appearance. His theory is based on the dissection of a child who died at the age of ten weeks and who had been diagnosed as having Treacher Collins Syndrome at birth. Their studies revealed bilateral abnormalities of the vascular supply to different parts of the face, besides the usual symptoms of MFD. From these facts, the vascular anomalies were extrapolated back to the prenatal period with the conclusion that the stapedial artery was the cause of the malformations seen in MFD. In the

same light, McKenzie (1958) hypothesizes a similar mechanism for Pierre Robin Syndrome, mandibular dysostosis, deformities of the external and middle ear, congenital deafness, cleft lip and palate, hypertelorism, and similar conditions that he considers "first arch syndromes."

Perhaps clarifying this relationship, Poswillo (1973), by studying animal models with branchial arch syndromes (first and second), showed that, while a developmental defect of the stapedial artery was not the initial cause of the disorders, a localized destructive hematoma did arise from the stapedial artery during its development. He found that the displacement and destruction of local mesenchyme by this expanding hematoma caused delays in differentiation of branchial arch structures and temporal bone. He concludes (Poswillo, 1974) that these observations provide strong evidence to support the contention that the faulty stapedial artery development could be considered a mechanism of malformation in hemifacial microsomia but not necessarily in MFD. Instead of a vascular mechanism, Poswillo (1975) places more credence on defects affecting the neural crest cells. Here it is hypothesized that central defects in the neural crest area, which by migration contribute to the formation of the branchial arches, are responsible factors in maldevelopment (Hövels, 1953*a*, 1953*b*). In this case focal death of preoptic neural crest cells would result in a spatial rearrangement and lack of ectomesenchyme of the first and second branchial arches, with the final result being abnormal symmetrical facial morphogenesis. McKenzie and Craig (1955) point out that there might be difficulties with this theory in that the most critically affected parts of the face—the zygomatic arch, the mandible, and the soft tissues—could have a predetermined status in the neural crest. However, this predetermination for a relative lack of structure would then be expected to result in a deficiency of *midline* structures and thus result in various clefts, which generally is not the case in MFD. It is also difficult to understand why defects in the ectomesenchyme derived from neural crest result in deformities of cartilaginous and osseous structures but not of dental structures. (Odontoblasts are believed to be derived also from ectomesenchyme.)

Thus, the timing of the pathogenic activity is placed anywhere from three to twelve weeks *in utero,* depending on the pathogenic mechanism explored and the number and expression of postnatal symptoms in each individual case description which have been extrapolated back to prenatal development. This extrapolation process inevitably leads to considerable speculation and confusion. Thus, description and discussion of etiology and pathogenesis have been limited to and by observations obtained from living individuals and autopsy material obtained from postnatal deaths.

Materials and methods

Clinical, radiographic, and histological studies were made of the heads of two male fetuses with similar head size and crown-rump length

(130 mm.). One specimen was diagnosed visually and radiographically as having the characteristics of MFD. A whole-body radiograph of this MFD fetus was compared to whole-body radiographs of 26 presumed normal fetuses of approximately the same crown-rump length. From this group, a fetus which was approximately the same size and developmental age as the MFD fetus was selected for comparative histologic examination. In this way, a comparison between normal and abnormal fetuses at the same developmental level is implied.

After photographs and lateral and posteroanterior radiographs had been made of the heads of the MFD fetus and the presumed normal fetus, the two heads were removed, bisected along the median plane, decalcified, embedded in celloidin and sectioned at 20μ. For both specimens, sections were made in the sagittal plane on the right side and in the frontal plane on the left side. The tissue sections were alternately stained with hematoxylin and eosin, Masson's trichrome and PAS.

No family or medical history was available on either fetus used in this study.

Results

CLINICAL EVALUATION. The abnormal fetus clearly exhibited the typical characteristics of mandibulofacial dysostosis. Even at 130 mm. (15 weeks), the characteristic "bird face" was evident to a certain degree

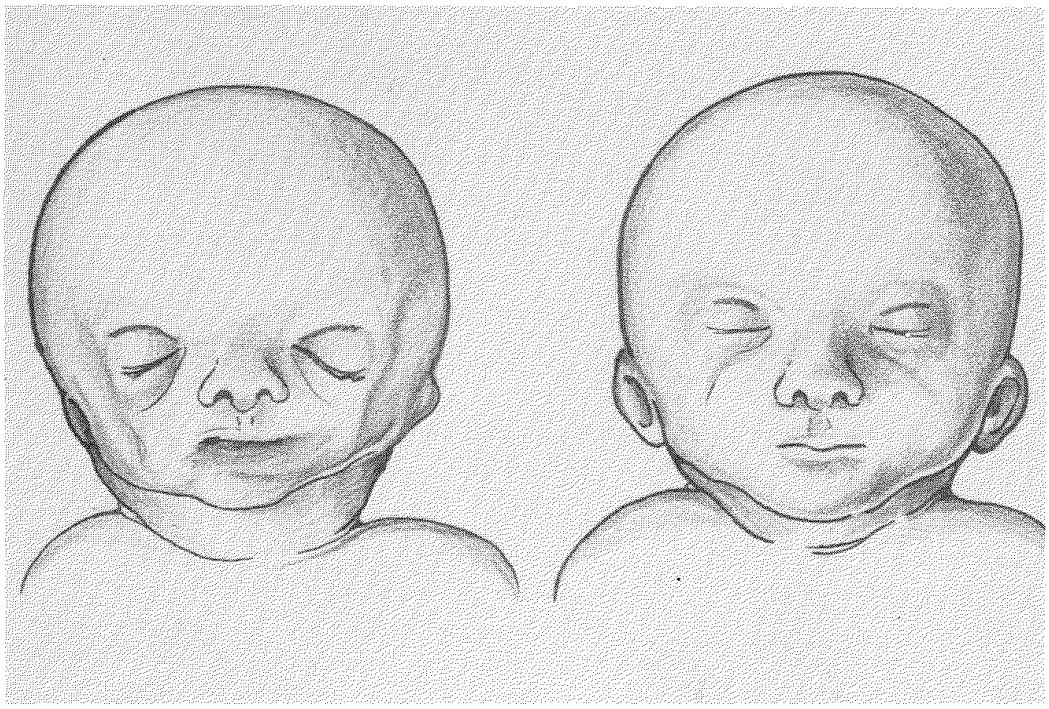

FIGURE 1A. (left) MFD fetus (130 mm.), frontal drawing. Note the "bird face," antimongoloid palpebral fissures, bilateral depressions in the region of the malar bones. Figure 1B. (right) Normal fetus (130 mm.), frontal drawing.

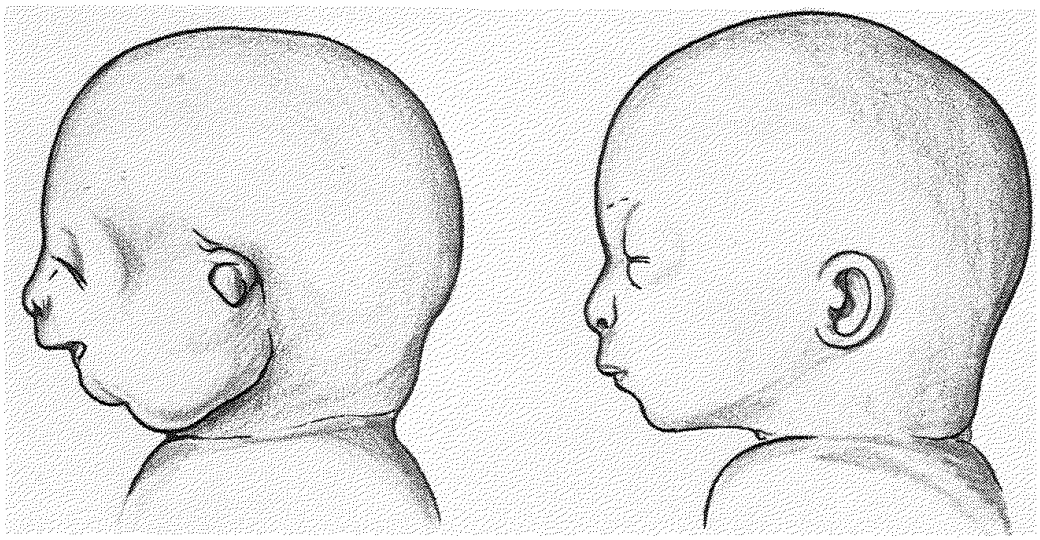

FIGURE 2A. (left) MFD fetus, lateral drawing (left side). Note the position and shapes of the auricles, the retruded mandible and convex facial profile. Figure 2B. (right) Normal fetus, lateral drawing.

(Figures 1 and 2). Although the malformations were present bilaterally, they were especially pronounced on the left side.

Eyes. There was antimongoloid obliquity of the palpebral fissures with a deep depression below and lateral to each eye. Notching (coloboma) of the lower eyelid was apparent on both sides. Deficiency in the eyelashes could not and would not be expected to be noted at this age under clinical evaluation. Deficiency of the lacrimal puncta also could not be discerned.

Maxilla. Bilateral depression of the malar bones resulted in a sunken appearance of the cheeks on both sides. Considerable deficiency in the midfacial height in the maxillary region resulted in a "squashed" appearance of the midface when compared to the normal fetus (Figures 1 and 2). The straightness of the nasofrontal angle also contributed to this appearance. Macrostomia was not noted.

Ears. The auricles were grossly deformed bilaterally (Figures 1 and 2), with only a rudimentary helix lying as a curved ridge, flattened close to the skin and protruding in an anterior direction. There was also no apparent external auditory meatus associated with either ear. Both ears were located more inferiorly than were those of the normal fetus. The right ear rudiment was smaller than the left. Pre-auricular hair elongation and deafness, of course, could not be discerned at this age, but based on other observations (see below) severe conductive hearing loss would have been inevitable.

Mandible. The chin was badly formed and severely retruded (Figure 2), apparently due to extreme shortening of the mandible (micrognathia). Open bite and malocclusion could not, of course, be discerned at this age.

RADIOGRAPHIC EVALUATION. Radiographically, the most notable features of this case of MFD were the size, shape, and position of the mandible and the absence of the zygomatic bones (Figure 3).

Cranium. The digital markings were somewhat pronounced as compared to the normal. The zygomatico-temporal bones appeared deficient. The straightness of the nasofrontal angle was readily apparent, as was a slight kyphosis of the cranial base.

Midface. The zygomatic bones were grossly underdeveloped with bilateral symmetrical deficiencies of the zygomatico-temporal and zygomatico-maxillary processes and almost complete absence of the intervening portion. The frontal processes of these bones constituted the lower lateral portions of the orbits on both sides and continued into small temporal processes which did not form complete bony arches with the zygomatic portions of the temporal bones. This deficiency resulted in an oval shape of the orbital rims on both sides.

The palatal structures were deficient in size, resulting in a shortness of the vertical dimensions of the maxilla. The maxilla was hypoplastic and filled with developing dental organs.

Mandible. The shape of the mandible was probably the most distinctive feature characterizing this case. The mandible was symmetrically and bilaterally shortened in body length and ramus height, probably due to bilateral failure of growth of the rami, bodies, and condyles. This resulted in a severe retrusion of the lower face and a generalized convexity of the facial profile. The gonial angle was clearly more obtuse than in the normal fetus, and the condylar heads and coronoid processes were bilaterally malformed and deficient. The mandibular body displayed the characteristic peculiar broad curvature considered by Pruzansky (1968, 1969) to be a most diagnostic feature of MFD.

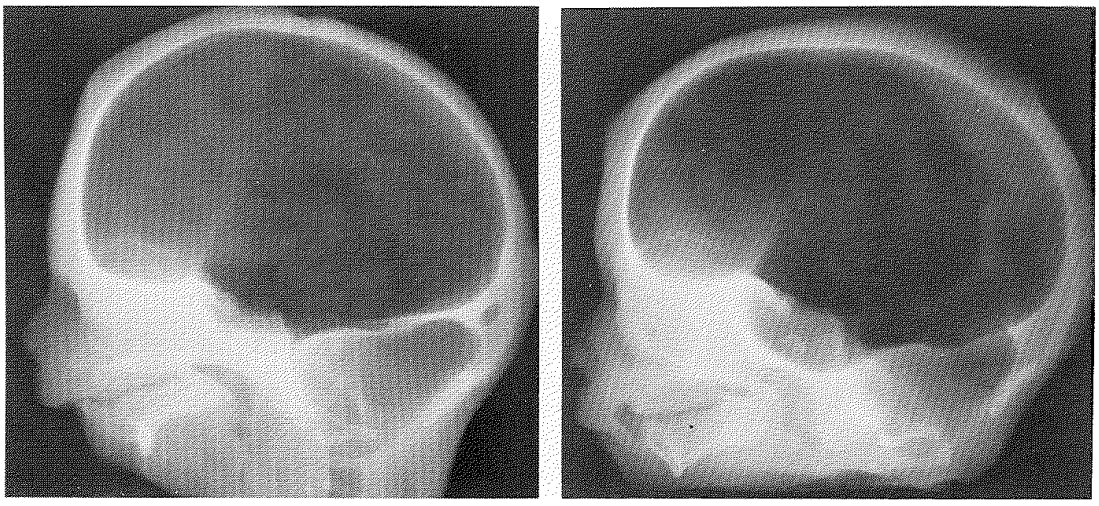

FIGURE 3A. (left) MFD fetus, half skull lateral radiograph demonstrating the shape and position of the mandible and cranial base. Figure 3B. (right) Normal fetus, half skull lateral radiograph.

HISTOPATHOLOGICAL EVALUATION. The histological analysis (Table 2) served to confirm the presence of the abnormalities observed in the clinical and radiographic examination.

Cranium. The zygomatico-temporal bone formation was deficient, and the nasofrontal angle was relatively straight when compared to the

TABLE 2. Histopathological characteristics of Mandibulofacial Dysostosis in the present case (fetus EH 821). Key: (+), symptoms present; (−), symptoms absent; (*), impossible to determine due to later development or difficulties in diagnosis.

histopathological craniofacial features of MFD	*fetus EH 821*
Ossification Defects	
zygomatico-temporal	+
zygoma	+
zygomatico-maxillary	+
maxillary	+
mandibular	+
ramus	+
body	+
coronoid	+
TMJ	+
palatine	+
mastoid process	*
styloid process	*
Cartilage Defects	
auricular	+
ossicles	+
inner ear	−
external auditory canal	+
cranial base	+
sella turcica	+
nasal conchae	+
Meckel's	+
Muscular Malformations	
temporal	+
masseter	+
zygomatic	+
pterygoids	+
Glandular Malformations	
submandibular	+
parotid	+
sublingual	+
Meibomian	*
lacrimal	*
Soft Tissue Defects	
antimongoloid slant of palpebral fissures	+
coloboma of lower eyelid	+
eyelash follicles of lower lid	+
atresia of lacrimal puncta	*
macrostomia	*
pre-auricular hair follicle formation	*
Miscellaneous Defects	
generalized hypervascularization	+
defective dental lamina formation	−

normal. The cranial floor was considerably retarded in osseous development. The cranial floor thus consisted of variously shaped cartilaginous elements whose position resulted in an acute cranial base angle.

Ears. The auricular cartilages were badly formed, and there was stenosis or absence of the external auditory meati. The tympanic membrane was absent or indefinable. The ossicles were not present in any recognizable form, although cartilaginous islands of indistinguishable shape were present in the location normally occupied by the malleus, incus, and the stapes. The distal end of Meckel's cartilage showed no evidence of differentiation into a definable malleus and incus. Inner ear structures were present and appeared unaffected. The Eustachian tubes were not patent.

Midface. Ossification in the maxilla was random and sparse with high vascularization noted, and thus the developing maxilla appeared hypoplastic. Deficiencies in zygoma ossification were evident in both the lateral and frontal sections (Figures 4, 5 and 6). There also was a deficiency of the masseter muscle mass in association with the deficiency of the zygomatic arch. Masseter muscle present appeared fused to the temporalis, which has been previously reported (Lockhart, 1929). This fact could account for some of the sunken appearance of the cheeks seen in the clinical examination. In contrast, the parotid and submandibular glands appeared to be grossly hyperplastic (Figures 4 and 5) relative to the normal fetus.

The downward slant of the eye noted in the clinical examination was clearly evident (Figure 7). Follicles for the lower eyelashes were absent from the medial two-thirds of the eyelid. The coloboma of the lower lid was observed as an accessory union of the eyelid (Figure 8).

The nasal conchae were short and malformed (Figures 6 and 7). The palatine bones were not completely formed along their midline union and soft tissue appeared to have filled in this void. This relationship

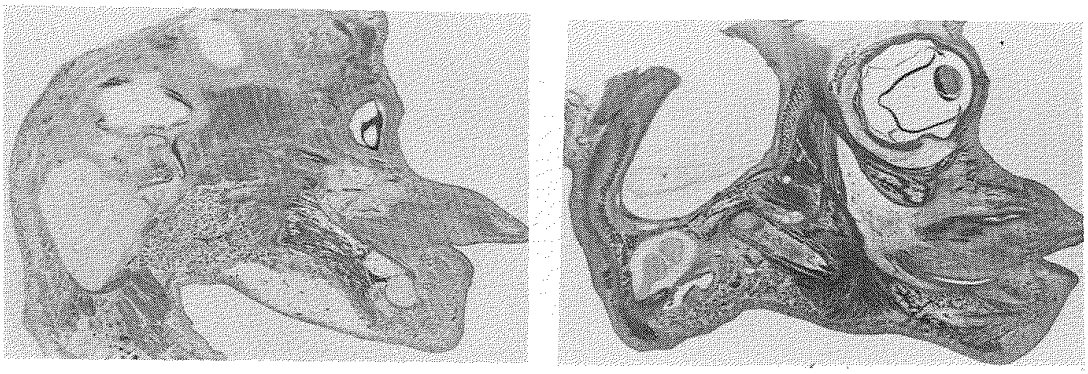

FIGURE 4A. MFD fetus, sagittal histologic section at the lateral aspect of the mandible. Note the hyperplasia of the parotid gland and the angulation of the muscles attached to the mandible. No ossicles are evident. Only a small spicule of bone represents the zygoma. Figure 4B. Normal fetus sectioned at approximately the same level, demonstrating the normal relationships of the zygomatic arch, ear ossicles and masseter and temporalis muscles.

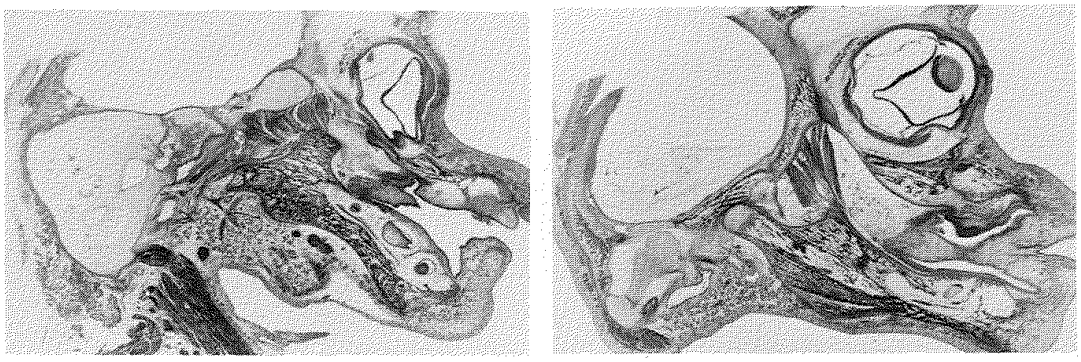

FIGURE 5A. (left) MFD fetus, sagittal section through the midportion of the mandible, which demonstrates the lack of condylar, ossicle and zygomatic formation. Note also the condition and location of the salivary glands and lymph nodes in relation to the broad curvature of the body of the mandible. Abnormal shape and retarded ossification of the cranial cartilages are also apparent. Figure 5B. (right) Normal fetus at approximately the same level of section.

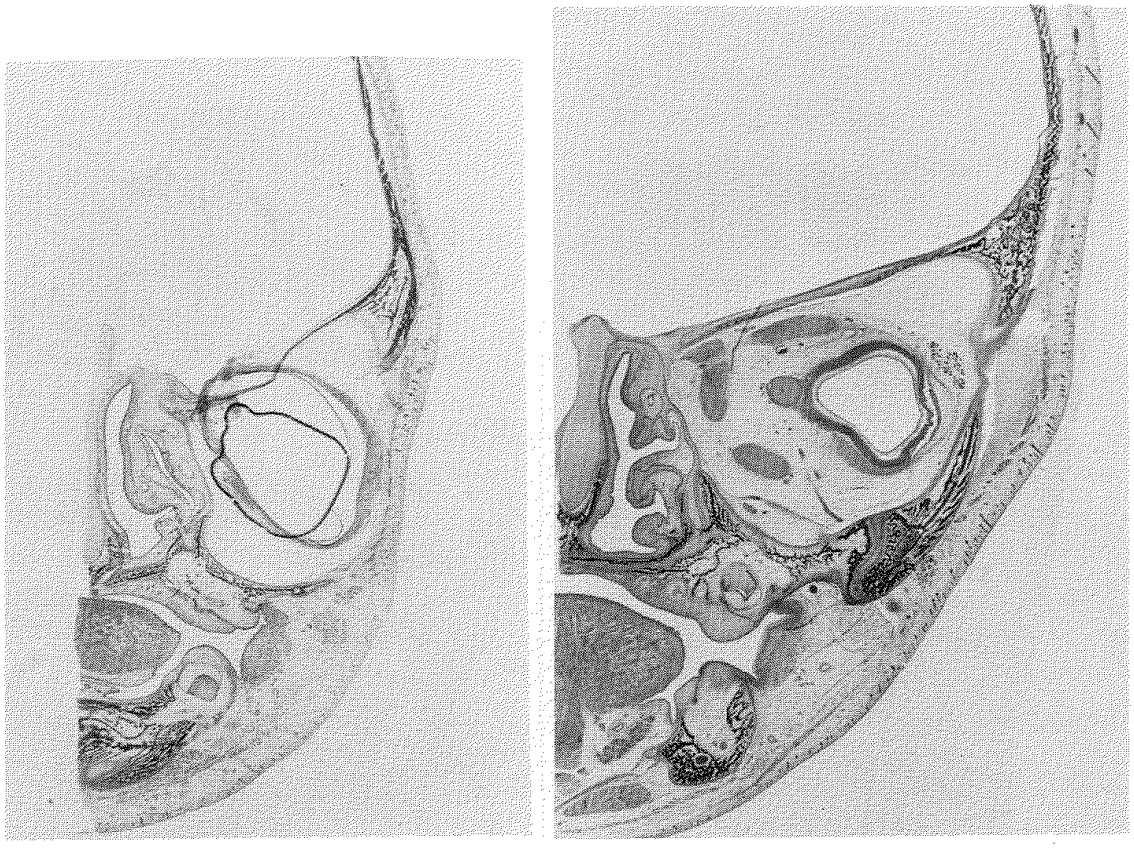

FIGURE 6A. (left) MFD fetus, frontal section, at the level of the posterior part of the orbit, demonstrating the lack of development of the zygomatic processes of the maxilla and temporal bones and the absence of the intervening zygoma. Figure 6B. (right) Normal fetus at the same level.

between hard and soft tissue may have reflected the presence of submucus cleft of the palate.

Mandible. The mandibular tissues, by far, showed the most abnormal development. As noted in the previous descriptions, the ascending

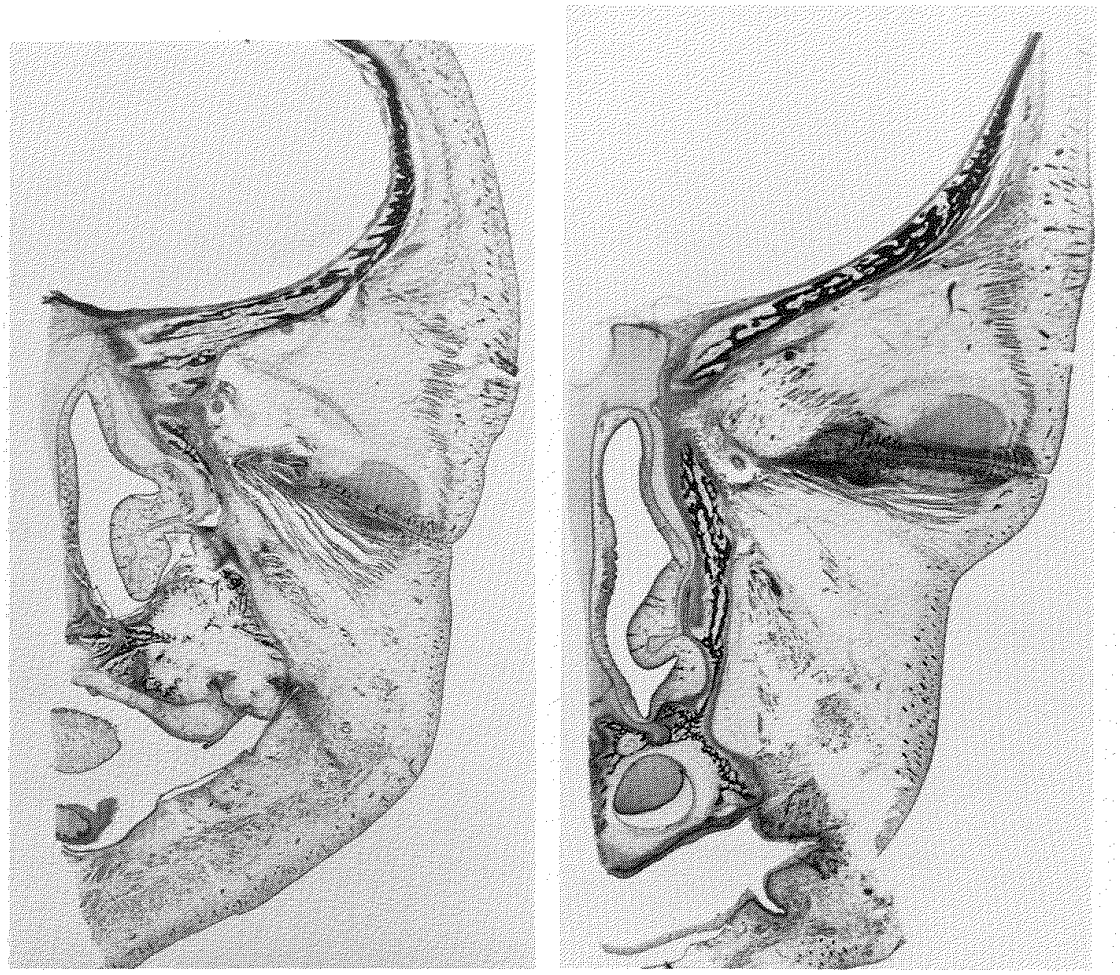

FIGURE 7A. (left) MFD fetus, frontal section at the level of the eyelid. This section demonstrates the slant of the eyelid. Note especially its relation to the surface topography. The eyelash follicles are also deficient in the medial two-thirds of the lower eyelid. Figure 7B. (right) Normal fetus.

ramus and the body of the mandible were short and abnormally formed, resulting in the receding lower facial appearance (Figures 4, 5 and 9). There appeared to be minimal secondary condylar cartilage formation on one side (Figure 10), with none on the other side (Figure 9), and thus no "growth cone" as observed in the normal series. With the lack of condylar formation and the associated articular disk, there was a displaced attachment of the pterygoid musculature (Figure 10) and apparent fusion with the temporalis muscle. The coronoid ossification was also affected, in that it presented an abnormally broad shape (anterioposteriorly and mediolaterally) for the attachment of the temporal musculature (Figures 5 and 11). The gonial angle was obtuse and appeared posteriorly located, perhaps due to masseter muscle deficiency and abnormal muscle attachment, lack of condylar growth, posterior positioning of the articular surface in relation to the acute cranial base, or a combination of these factors.

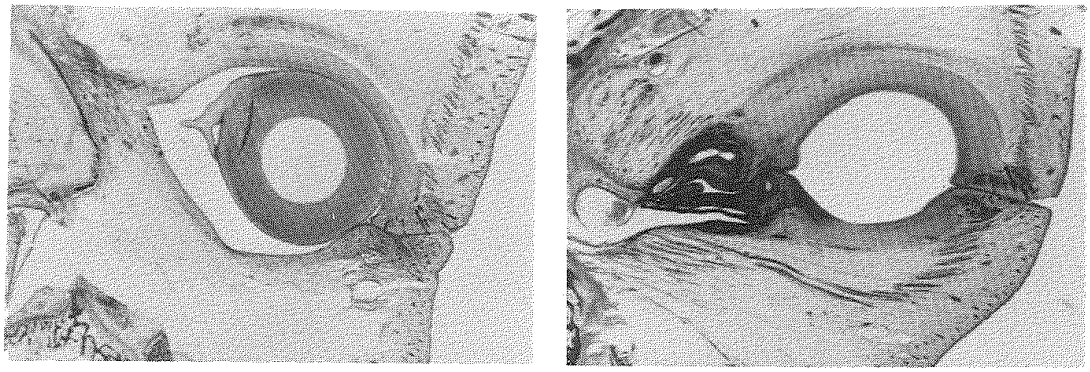

FIGURE 8A. (left) MFD fetus section demonstrating the accessory union (coloboma) of the lower eyelid. Figure 8B. (right) Normal fetus.

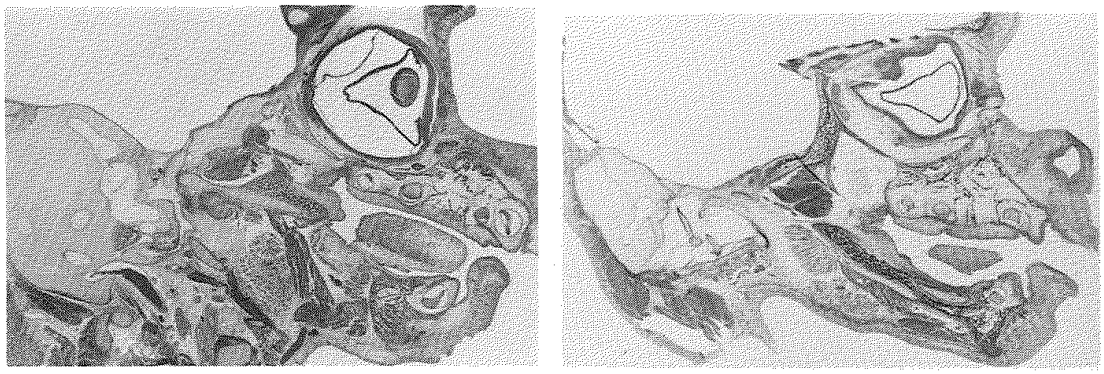

FIGURE 9A. (left) MFD fetus, sagittal section at the medial level of the mandible. Meckel's cartilage appears to be functioning as an articular process. Delayed development of the chondrocranial structures is evident. Figure 9B. (right) Normal fetus demonstrating the normal position (medial to the mandible) and relative size of the submandibular salivary gland.

The distal end of Meckel's cartilage was totally undifferentiated (on one side) into the ear ossicles and appeared to be functioning as an articular component because of the lack of the secondary cartilage of the condyle (Figure 9). Because of the bilateral temporal and zygomatic deficiencies, no glenoid fossa could be seen (Figure 10).

The body of the forming mandible was one of the most distinctive features seen in the mandibular region. Very little ossification was occurring in the "bowed" region, and Meckel's cartilage was "bent" convexly upward. Of particular interest was that ossification, where present, was taking place around or above Meckel's cartilage, rather than laterally to it (Figure 12). Concomitantly, in this area, the submandibular salivary glands were greatly enlarged and laterally positioned, corresponding to a high degree with the curvature of the lower border of the body of the mandible, and causing a bulging of the soft tissue covering the lower border of the mandible (Figures 4, 5, 10 and 11). There were also enlarged lymph nodes in this location (Figure 5).

Vascularization of the tissues in the mandible and midface, while expected to be somewhat deficient, appeared to be much more extensive than that observed in the normal fetus.

Discussion

Dysmorphogenesis in Mandibulofacial Dysostosis exists as a continuum of abnormal development from conception until postnatal growth has concluded. In contrast to previous reports, the present study is able to compare human fetuses with Mandibulofacial Dysostosis to a presumed normal fetus at a stage of development (130 mm. — 15 weeks) that is close to the presumed time when the strongest aberrant development takes place. Thus we are describing anomalies of the craniofacial region at a point in time when the facial structures have just developed and are growing and interacting among themselves. In this way, a clearer picture of the pathogenesis of Treacher Collins Syndrome should result than is possible from that obtained by prenatal extrapolation of postnatal symptoms. In the latter instance, it is likely that the original or more direct anomalies are obfuscated by further development in terms of growth and compensatory adjustments in the facial components.

The prenatal symptoms of the case of Treacher Collins Syndrome discussed in this study, however, correlate to a high degree with pre-

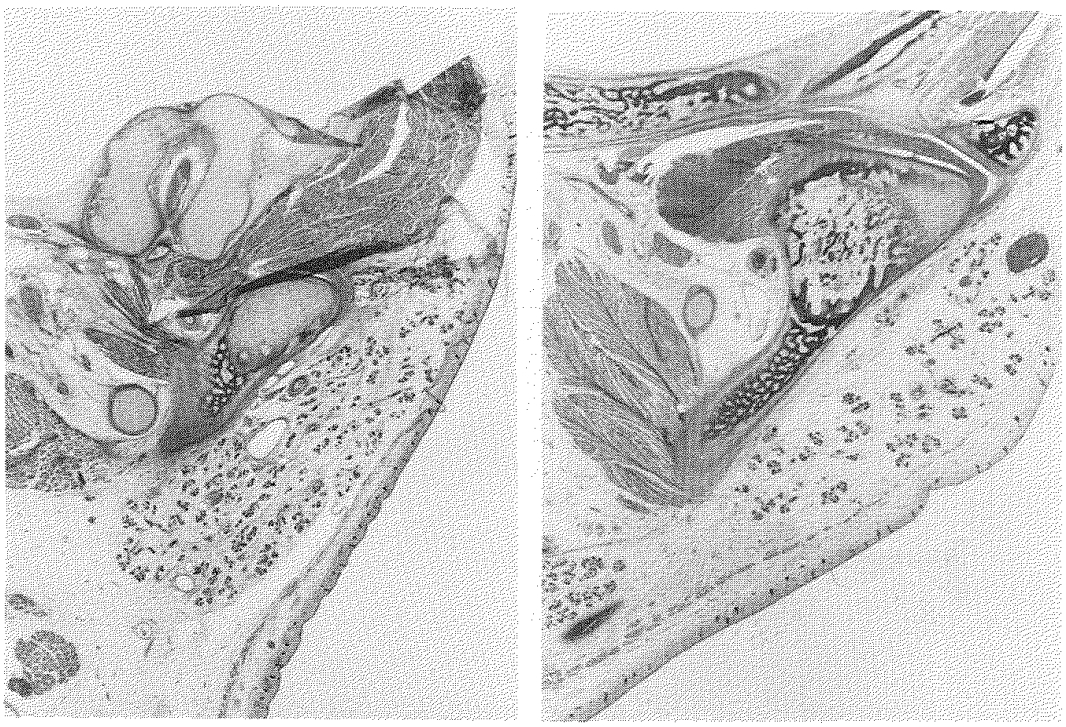

FIGURE 10A. (left) MFD fetus, frontal section showing the condylar relationships. Condyle formation on this side (left) is minimal. Note the salivary gland hyperplasia, lack of TMJ formation, attachment of the lateral pterygoid to the medial aspect of the condyle and apparent fusion of the other head of the lateral pterygoid to the temporalis muscle. (Artefact fold in the condylar region.) Figure 10B. (right) Normal fetus. Note that lateral pterygoid attaches to the condylar cartilage and the articular disk.

vious descriptions in the literature. The "obligatory" symptoms, as discussed by Axellson et al. (1963) and Roberts, Pruzansky, and Aduss (1975), such as antimongoloid palpebral fissures, colobomas of the lower eyelid, eyelash malformations, zygomatic defects, otic defects, and peculiar mandibular abnormalities are clearly evident in the present case and thus should be regarded as the most direct results of the pathogenic activity. Other common symptoms, e.g., kyphosis of the cranial base, malocclusion, open bite, and sinus abnormalities, while useful for clinical diagnosis, must be considered as indirect compensatory growth adjustments that are secondary to the more direct retarded development and defects of the cranial base region, the mandible, the zygomatic arch, etc. This perspective is necessary if an accurate standardization of diagnostic criteria and detection of the pathogenesis is to be accomplished.

PATHOGENIC TIMING. While any individual case description is not in itself an indication of the complete pathogenic sequence, several conclusions may be reached as to the timing of developmental defects relating to the expression of this case of MFD. It is apparent by involvement of the mandible, external ear, and stapes that the complete form of MFD in this case involves the first and second branchial arches and intervening tissue, and thus represents a monotopic malformation syndrome.

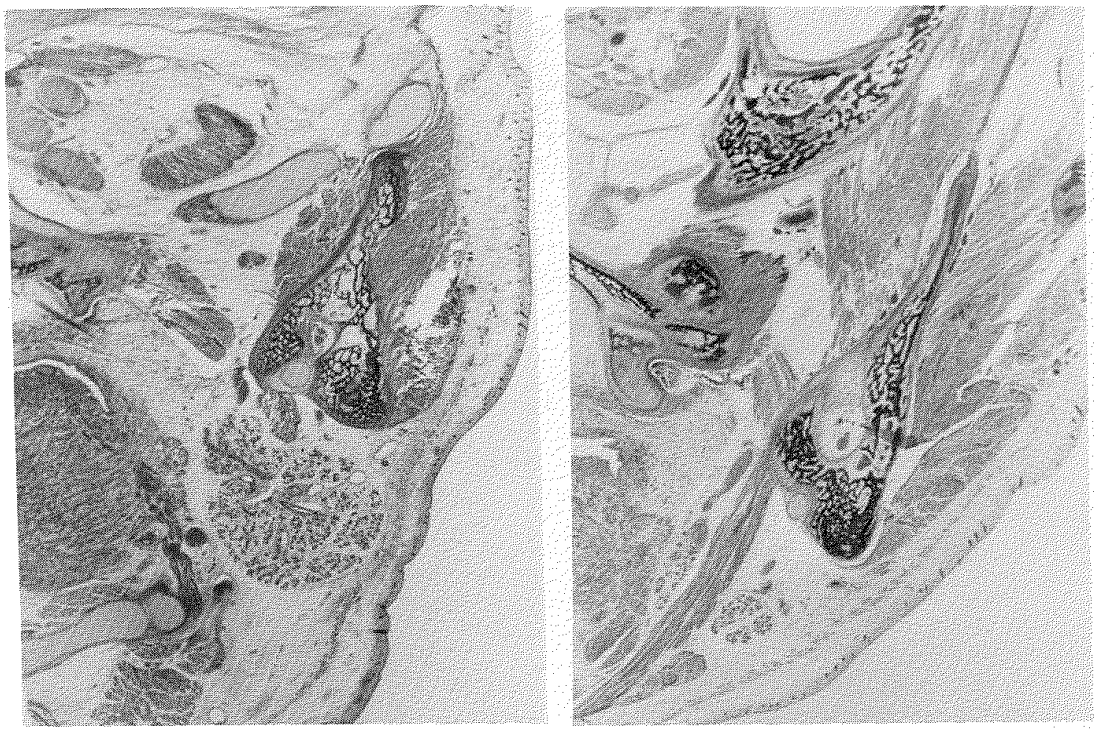

FIGURE 11A. (left) MFD fetus, frontal section in the region of the mandibular "bow" and the highest extent of the coronoid process. Note again the position and hyperplasia of the submandibular salivary glands, the ossification of the mandible in relation to Meckel's cartilage and the absence of the zygoma. Figure 11B. (right) Normal fetus at the same section level.

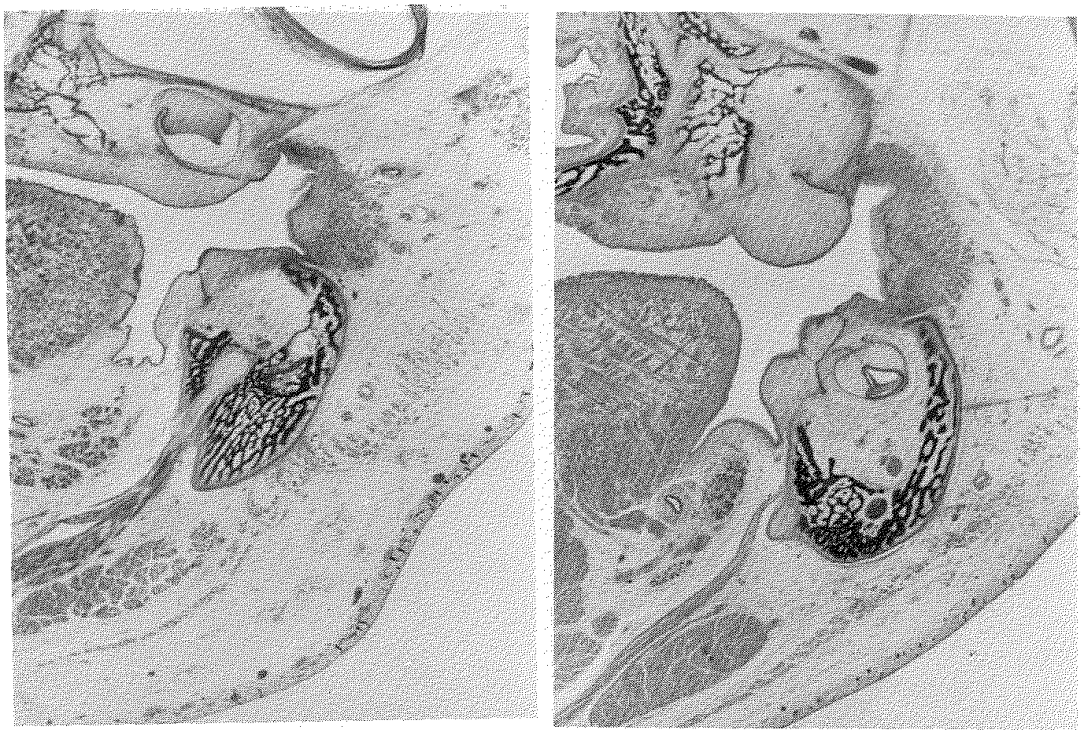

FIGURE 12A. (left) MFD fetus, frontal section (frontal to the mandibular "bow"). Ossification of the mandible is occurring around Meckel's cartilage. The mylohyoid muscle appears to be inserting directly onto Meckel's cartilage. Figure 12B. (right) Normal fetus.

It is also apparent that all the major aspects of this syndrome (Table 1) are at full expression by 130 mm. (15 weeks). The defects noted indicate the retardation or failure of differentiation occurred in the second month of pregnancy. The bones of the face most notably affected are the zygomatic arches which begin ossification at six to seven weeks (O'Rahilly and Gardner, 1973). Since there is no real evidence of differentiation of the zygomatic arch in the present case, and since there is only partial, abnormal differentiation of the mandible, it would appear that the defect appears primarily at about seven weeks of age.

This is also a critical time for the formation of the external ear. At six weeks, the external auditory meatus is flanked on each side by three hillocks derived from the mandibular and hyoid arches. At seven weeks, the rudimentary ear is being formed. Also, by this time the eyes have developed and "rotated" nearly to their final position, the eyelids are not present, and the eyes are wide open. The deficiency of eyelid formation (coloboma) would place the defect at or after seven weeks, when the lid is forming.

Additional evidence for the defect appearing at about seven weeks can be derived from Table 1. Secondary or less frequently reported symptoms (in this case and in the literature), such as flat parieto-occipital bone, atresia of the lacrimal puncta, external auditory canal defects, pre-auricular hair elongation, hypertelorism, cleft palate, TMJ malformations, etc., would appear to point to the appearance of the primary

developmental defect at about seven weeks and to indicate that the defects occurred within a range of time such as six to eight weeks, rather than as a single event causing the defects. The variability of the individual cases reported would also indicate that severity of the symptoms encountered correlates with the time of appearance and severity of the primary defect(s). It must be pointed out that, while the duration of the appearance of the primary defects *could* extend perhaps to ten weeks, it is unlikely that any defects appeared before six weeks of age. This conclusion is based on the lack of any reported structural dental defects. The timing suggested correlates well with the observations made by Franceschetti and Klein (1949) and Briggs (1952) and is slightly earlier than the time suggested by Mann (1943) and Harrison (1951).

PATHOGENIC MECHANISMS. The mechanisms responsible for MFD still cannot be clearly delineated. However, retarded development and ossification abnormalities suggested by Franceschetti and Klein (1949) and Briggs (1952) are clearly present in this case and appear to provide a possible index to the mechanism responsible for the hard tissue defects seen postnatally. Together with the obvious deficiencies in zygomatic and mandibular ossification and retarded development of the cranial base, there appear to be general, although not extreme, ossification abnormalities and retarded development of *all* of the *intramembranous bones* of the skull. This is exemplified to some extent by the abnormally located intramembranous ossification of the mandible which, in this case of MFD, is taking place *around* the abnormally shaped Meckel's cartilage rather than *lateral* to it, as is normal. A scheme such as this would account for almost all of the frequently and less frequently observed bony defects, such as flat parieto-occipital bone, malar defects, mandibular defects, maxillary hypoplasia, palatine deficiency, high palate, accentuated digital markings, mastoid hypoplasia, straight nasofrontal angle, etc. Difficulties with this scheme would be encountered in explaining the soft-tissue defects of the eye and ear. A possible explanation to overcome this difficulty might be that, although the syndrome mainly involves genetically determined target areas of the first and second visceral arches' mesodermal migration, it is possible that related abnormalities such as ossification defects in the intramembranous bone formation might play a role in the extent of the expression of MFD.

In this same regard, the defect of the body of the mandible, although probably explained by ossification defects around an abnormally shaped Meckel's cartilage, appears to be related to the hyperplastic and misplaced salivary glands and lymph nodes which positionally and volumetrically correspond to the broad curvature defect of the cartilage and bone of the mandible. It should be remembered at this point that membranous bones of the face are considerably "plastic" in response to physical forces (c.f. orthodontics, orthopedics, and deleterious effects of the Milwaukee brace), and the relationship here could reflect osseous defects as the result of overgrowth of contiguous soft tissues. It is

particularly interesting to note the *hyper*plasia of these glands and adjacent vascular system in a malformation syndrome where *hypo*plasia is the general rule. Since the primordia of the parotid and submandibular glands appear during the sixth week *in utero* and the sublingual gland during the seventh week (Sicher, 1966), it is attractive to speculate a causal relationship between the hyperplasia of the salivary glands and the regions of the primary defects of this malformation syndrome.

One could speculate further in trying to determine the cause of such salivary gland hyperplasia. While an endocrine imbalance, a defect in glycoprotein metabolism, antigen-antibody reaction between mother and child, or a genetic control are possible causes, such hyperplasia could be caused by a defect in the development of the nervous system, possibly the sympathetic in this case. In this same regard, it is known that the migration of mesoderm could be interpreted as following the influence of the growing nervous system. Likewise, it has been shown that the initial site of ossification bears a consistent relationship to a particular location along a particular nerve (O'Rahilly and Gardner, 1973). In essence, then, the thought put forth is that the original defect could be manifest in the character and position of the developing nervous system. This in turn could cause three (or more) complementary and synergistic abnormalities: that of the gross salivary gland hyperplasia, abnormal mesodermal migration, and abnormal position of the initial ossification sites. It is then possible to theorize that a defect in such neural growth might affect the final distribution of mesodermal structures (like Meckel's cartilage), the ossification, and the resultant shape of the facial component in the same manner as McKenzie (1958) explains the defects on the basis of vascular anomalies.

It must be noted, however, that no postnatal sensory or motor nerve defects have been noticed and reported in conjunction with MFD, save for one report indicating the absence of the chorda tympanii and greater superficial petrosal nerves (Sando, Hemenway, and Morgan, 1968). Likewise, it must be noted that no such positional and volumetric abnormalities of the salivary glands and lymph nodes have been noticed and reported in the literature dealing with postnatal autopsy material and survivors. However, it is possible that this condition might not be present postnatally (salivary gland absence has been reported by McKenzie and Craig [1955]). Attractive as this speculation is, it must be remembered that, while salivary gland hyperplasia might explain the cause of some of the regional distortions, this might be just another effect of some other original anomalad.

Vascular anomalies, suggested by McKenzie (1958) as the initial event (anomalad) in the pathogenic sequence of MFD, cannot be ruled out by this study. Vascular abnormalities of the stapedial artery occurring in the fifth to sixth week are a possible explanation of the pathogenic sequence in that they could explain defects of the ear and maxilla. Difficulties with this explanation are encountered, however, in that

these abnormal vascular events take place between the third and fifth weeks, before ossification centers occur in the mandible or maxilla (sixth week) and before the appearance of the auricular hillocks (sixth week). The ability of synchronous *bilateral* vascular defects appearing is also doubtful. Also, it might be expected that a defect of the stapedial artery would in some degree affect the stapes. In this regard, McKenzie (1958) points out that the ossicles are seldom abnormal in an otherwise normal ear but that, if there is an abnormality, it is usually the stapes which is at fault. But in MFD, it is the stapes which is the least affected of the ossicles (Scheer, 1967; Fernandez and Ronis, 1964; Sando, Hemenway, and Morgan, 1968; Stark and Saunders, 1962; Briggs, 1952), and even deafness is not a constant finding in MFD. It is also particularly perplexing that there is a conflict in McKenzie's own writing as to whether the stapes and incus were *absent,* as reported originally in 1955, or whether they were *normal,* as reported in 1958 while citing the original study of 1955. It should also be noted in this respect that subsequent articles, discussing this argument and citing McKenzie and Craig (1955), stated that McKenzie and Craig showed evidence of a defect of the stapedial artery (Rogers, 1964). It must be remembered that the stapedial artery disappears at about six weeks *in utero* and that the cited study was performed on an infant who died at ten weeks *post partum.* It is, therefore, impossible to draw such a conclusion. Also, it is impossible to determine whether vascular abnormalities are the *cause* of the syndrome or just another *effect* of this malformation syndrome that is caused by some unknown initial event (anomalad).

The present case of MFD, which showed more extensive vascularization of the tissues, tends to point to alternate explanations but by no means refutes McKenzie's contentions.

ETIOLOGY. Although no pertinent patient or family history is available in this case, it is well established in the literature that the events occurring in this syndrome are under some structured genetic control. Whether their expression is directed at generalized mesodermal migration or differentiation processes, vascular, nervous, ossification or some other mechanisms cannot be discerned as yet. Coincidentally, it must be stressed that exogenous environmental factors affecting the mother during the first trimester of gestation could have some influence on the genetic expression, penetrance, or apparent or sporadic appearance of the defects associated with MFD (Granrud, 1953; Poswillo, 1975). The plethora of reports of various nervous shocks and maladies, although seemingly unrelated by scientific reasoning, causes one to muse over the association possibilities.

These data raise the possibility that in suspected families, as an adjunct to genetic counseling, prenatal diagnosis of Treacher Collins Syndrome may be possible. Such diagnostic measures might include fetal radiographs, maternal blood chemistry, or amniocentesis determination of glycoprotein titer as an indicator of hyperplasia of the salivary glands. It is also possible that, in cases of apparent sporadic appearance of the

syndrome, examination for subclinical carrier status could be accomplished, using salivary gland status and radiographic examination of the mandible, maxilla, and cranial base regions as the basis for such an examination. Further studies will be necessary to determine the feasibility of these various diagnostic techniques.

Summary and conclusions

The visual, radiographic, and histopathologic findings on a 130 mm. (15 weeks) fetus with MFD were described and compared with a presumed normal fetus of approximately the same size and developmental age. The most striking abnormalities were:

1. *Eyes:* antimongoloid palpebral fissures with coloboma of the lower eyelid and eyelash follicle deficiencies.
2. *Ears:* auricular and external auditory deformities, together with defects of the ossicles.
3. *Mandible:* striking abnormal shape, size, and position of the components of the mandible, together with defective formation and growth of the condyle.

Findings in the MFD fetus did not differ significantly from those in postnatal survivors previously described in the literature; that is, the major phenotypic signs and symptoms of MFD are present even at this early developmental stage.

The critical period of pathogenic activity leading to the deformities was placed at about seven weeks *in utero,* most likely caused by a complex deficiency in differentiation, ossification, and defective interaction of the structures of the first and second branchial arches. Salivary gland-nervous system abnormalities were discussed as a possible initiator of the pathogenic sequence. Vascular deficiencies were not noted. While it appeared that the etiology was clearly genetic, previously reported exogenous factors were suggested as playing a part in the genetic expression of the defect. The findings in this study have possible clinical diagnostic applications and these are discussed.

Acknowledgments: The specimens used in this study were obtained from the Bradley M. Patten Embryology Research Collection of the Department of Anatomy, The University of Michigan, Ann Arbor. Drawings by William L. Brudon.

reprints: *Dr. Rolf G. Behrents*
Center for Human Growth and Development
University of Michigan
Ann Arbor, Michigan 48109

References

AXELLSON, A., BROLIN, I., ENGSTROM, H., and LIDEN, G., Dysostosis mandibulofacialis, *J. Laryng. Oto., 87,* 575–592, 1963.

BRIGGS, A. H., Mandibulo-facial dysostosis, *Br. J. Ophthal., 37,* 171–176, 1952.

CAMPBELL, W., The Treacher-Collins syndrome, *Br. J. Radiol., 27,* 639–641, 1954.

FERNANDEZ, A. O., and RONIS, M. L., The Treacher-Collins syndrome, *Arch. Otolaryng., 80,* 505–520, 1964.

FRANCESCHETTI, A., and KLEIN, D., The mandibulo-facial dysostosis, a new hereditary

syndrome, *Acta Ophthal., 27,* 141–224, 1949.
GRANRUD, H., On the etiology of dysostosis mandibulo-facialis, *Acta Ped., 42,* 499–505, 1953.
HAMILTON, W. J., BOYD, J. D., and MOSSMAN, H. W., Human Embryology, Baltimore: Williams and Wilkins, 1962.
HARRISON, S. H., Treacher Collins syndrome, *Br. J. Plast. Surg., 3,* 282–290, 1951.
HERBERTS, G., Otological observation on the "Treacher Collins syndrome", *Acta Otolaryng. Stockh., 54,* 457–465, 1962.
HÖVELS, O., Zur systematik der Missbildungen des erster visceralbogens unter besonderer berrucksichtigung der dysostosis-mandibulo-facialis, *Ztschr. Kinderheilk., 73,* 532, 1953*a*.
HÖVELS, O., Zur systematik der Missbildungen des erster visceralbogens, *Ztschr. Kingerheilk., 73,* 568, 1953*b*.
LANGMAN, J., Medical Embryology, Baltimore: Williams and Wilkins (1969).
LOCKHART, R. D., Variations coincident with congenital absence of the zygoma (Zygomatic process of the temporal bone), *J. Anat. Lond., 63,* 233–236, 1929.
MCENERY, E. T., and BRENNEMANN, J., Multiple facial anomalies, *J. Pediat., 11,* 468–474, 1937.
MCKENZIE, J., The first arch syndrome, *Archs. Dis. Child., 33,* 477–486, 1958.
MCKENZIE, J., and CRAIG, J., Mandibulo-facial dysostosis (Treacher Collins syndrome), *Archs. Dis. Child., 30,* 391, 1955.
MANN, I., and KILNER, T. P., Deficiency of the malar bones with defect of the lower lids, *Br. J. Ophthal., 27,* 13–20, 1943.
MOSS, M. H., SAPHIR, R. L., and GOTTLIEB, M. I., Mandibulo-facial dysostosis: report of two cases with chromosome analysis, *Am. J. Dis. Child., 107,* 304–307, 1964.
O'RAHILLY, R., and GARDNER, E., The initial appearance of ossification in staged human embryos, *Am. J. Anat., 134,* 291–308, 1973.
O'RAHILLY, R., and MEYER, D. B., Roentgenographic investigation of the human skeleton during early fetal life, *Am. J. Roent. Rad. Ther. Nuc. Med., 76,* 455–467, 1956.
PATTEN, B. M., The normal development of the facial region, in: Congenital Anomalies of the Face and Associated Structures, Pruzansky, S. (ed.), Springfield: Charles C Thomas, 11–45, 1961.
PATTEN, B. M., Human Embryology, New York: McGraw-Hill, 1968.
POSWILLO, D. E., The pathogenesis of the first and second branchial arch syndrome, *Oral Surg., Oral Med., Oral Path., 35,* 302–328, 1973.
POSWILLO, D. E., Orofacial malformations, *Proc. Roy. Soc. Med., 67,* 343–349, 1974.
POSWILLO, D. E., The pathogenesis of the Treacher Collins syndrome (mandibulofacial dysostosis), *Br. J. Oral Surg., 13,* 1–26, 1975.
PRUZANSKY, S., Postnatal development of craniofacial malformations, *J. Dent. Res., 47,* 936, 1968.
PRUZANSKY, S., Not all dwarfed mandibles are alike, Proceedings of First Conference on Clinical Delineation of Birth Defects, Part 2, Malformation Syndromes in Birth Defects: Original Article Series, D. Bergsma (ed.), New York: National Foundation, Vol. 2, 109–129, 1969.
ROBERTS, F. G., PRUZANSKY, S., and ADUSS, H., An x-radiocephalometric study of mandibulofacial dysostosis in man. *Archs. Oral Biol., 20,* 265–281, 1975.
ROGERS, B. O., Berry-Treacher Collins syndrome: a review of 200 cases, *Br. J. Plast. Surg., 17,* 109–137, 1964.
ROVIN, S., DACHI, S. F., BORENSTEIN, D. B., and COTTER, W. B., Mandibulofacial dysostosis, a familial study of five generations, *J. Pediat., 65,* 215–221, 1964.
SANDO, I., HEMENWAY, W. G., and MORGAN, W. R., Histopathology of the temporal bones in mandibulofacial dysostosis, *Trans. Am. Acad. Opthal. Otolaryng., 72,* 913–924, 1968.
SCHEER, A. A., Correction of congenital middle ear deformities, *Arch. Otolaryng., 85,* 269–277, 1967.
SICHER, H., Orban's Oral Histology and Embryology (6th edition), St. Louis: C. V. Mosby, 266–330, 1966.
SIEBNER, V. H., Dysostosis mandibulo-facialis, *Med. Klin., 58,* 90, 1963.
STARK, R. B., and SAUNDERS, D. E., The first branchial syndrome, the oral-mandibular-auricular syndrome, *Plast. Reconstr. Surg., 29,* 229–239, 1962.
STOVIN, J. J., LYON, J. A., and CLEMMENS, R. L., Mandibulo-facial dysostosis, *Radiol., 74,* 225–231, 1960.
SZLAZAK, J., Treacher Collins syndrome, *Canad. Med. Assoc. J., 69,* 274–276, 1953.
WALKER, D. G., Malformations of the Face, Edinburgh: Livingstone, 1961.