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Original Article

Multiple developmental origin of the upper incisor in mouse: histological and computer assisted 3-D-reconstruction studies

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ABSTRACT Heads of 11-15-day-old mouse embryos were cut in frontal serial sections. Early development of the maxillary incisor was analyzed using series of thick (5 and 7 μm) and semi-thin (1 μm) frontal sections and computer assisted 3-D-reconstructions of the epithelial component. The enamel organ of the mouse maxillary incisor was found to be a complex structure of multiple origin, involving several epithelial anlagen — primary dental laminae —, which could hypothetically correspond to the 5 upper incisors of early mammals. The transitory existence of at once distinct and then fusing dental primordia could reflect heterochronic changes in ontogeny which might be related to phyletic trends.

KEY WORDS: *mouse, incisor, development, three-dimensional reconstructions, heterochrony*

Introduction

The developing dentition provides us with an interesting tool to try to understand the control mechanisms of spatial organization and acquisition of complex morphologies, and to correlate ontogenic and phylogenic aspects. The problem of initial pattern formation during odontogenesis has been recently discussed by Lumsden (1988) and Ruch (1987, 1990), and the putative role of homeobox genes (msx 1 and msx 2) has been documented (Mackenzie *et al.*, 1991, 1992; Jowett *et al.*, 1993). Interpretation of *in situ* hybridization during initial steps of odontogenesis requires a perfect knowledge of the dynamic morphological aspects.

As far as the mouse maxillary incisor is concerned, classical data suggested that it corresponds to the median incisor (I_2) of the general eutherian dental formula (I_3, C, P_4, M_3), while the other two (I_1, I_3) have been lost during muroid evolution (Hershkovitz, 1967). However, Strassburg *et al.* (1970) have described three developing incisor anlagen (I_1, I_2, I_3) in mouse, the anlage I_2 giving rise to the functional incisor, anlagen I_1 and I_3 being lost very early during development.

In this paper we addressed the questions of whether mouse embryos recapitulate the incisor number (4-5) found in ancient fossil mammalian species (Ziegler, 1971) and whether the mouse maxillary incisor might result from the assembly of several initially distinct tooth primordia.

Serial sections of critically staged days 11-15 mouse embryos were analyzed performing computer assisted 3-D-reconstructions. The multiple origin of the maxillary incisor was demonstrated. We feel that such descriptive data constitute a prerequisite for further molecular approaches. Furthermore, such data are important as far as interpretation of ontogenetic-phylogenetic relationships are concerned.

Results

Definition of the analyzed structures

The analyzed area included the oral epithelium of the developing premaxilla and the adjacent part of developing maxilla.

The primary dental lamina (PDL) represented a longitudinal thickening of the oral epithelium formed by high basal cylindrical cells (long axes of their nuclei were oriented perpendicularly to the basement membrane) and several layers of flat superficial cells (long axes of their nuclei were oriented parallel to the surface) facing the oral cavity (Figs. 1 and 2A).

The secondary, i.e. composite, dental lamina was formed by a folded (arched) sheet of densely arranged cylindrical cells, forming a groove and by many layers of flat cells in this groove (Figs. 2B and 6). The arched area included several primary dental laminae (Figs. 2 and 3).

Abbreviations used in this paper: PDL, primary dental lamina; MPDL, middle primary dental lamina; wt.c., weight class; I, incisor; C, canine; P, premolar; M, molar.

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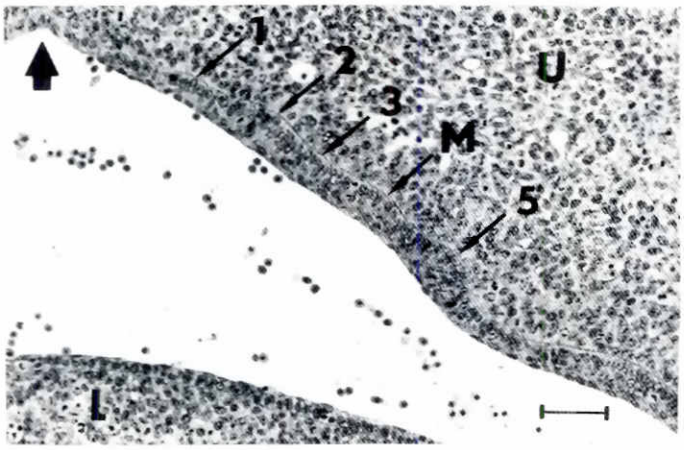

Fig. 1. Primary dental laminae (frontal section) in 11(24) mouse embryo, wt.c. 51-75 mg. *U, upper jaw; L, lower jaw. Large arrow indicates the middle line. Narrow arrows point to the primary dental laminae. M, the middle PDL; 1 and 2, the medial PDL 1 and 2, respectively; 5, the lateral PDL 5; 3, trace of the medial PDL 3. In this embryo, the lateral PDL 4 was not yet apparent. Bar, 50 µm.*

In 11(24) embryos (51-100 mg wt.c.), symmetrically, three groups of primary dental laminae could be distinguished (Figs. 1 and 4A,B):

a) The middle primary dental lamina (MPDL), which posteriorly fused with the epithelium of the anterior margin of the primary choana situated between the developing nasal septum and anterior pole of the palatal shelf.

b) Medial primary dental laminae located medially to the MDPL and indicated as the PDL 1, 2 and 3, in a medio-lateral direction.

c) Lateral primary dental laminae indicated as the DPL 4 and 5 in a medio-lateral direction: PDL 5 was located laterally to the most posterior part of the MPDL. PDL 4 appeared in developmentally more advanced embryos and was interposed between the MPDL and the anterior part of the PDL 5 (Fig. 6G-I).

The MPDL and the medial primary dental laminae tended to fuse in their most anterior parts (Fig. 4A,B).

In 12(12) embryos (76-100 mg wt.c.), the 3 groups of primary dental laminae were involved in the formation of the composite incisor dental lamina (Fig. 4C). In the posterior part, the crest of the composite dental lamina corresponded to the MPDL. The lateral PDL 4 and the medial primary dental laminae were engaged, respectively, in the formation of the lateral and medial slopes of the composite dental lamina.

The lateral PDL 5 was situated laterally to the posterior part of the composite dental lamina (Figs. 4C and 3A). In some embryos, the posterior end of the PDL 5 reached the maxillary outgrowth (Fig. 5).

In anterior direction a diminution of the lateral PDL 5 occurred and still more anteriorly also of the lateral PDL 4, while the medial primary dental laminae became more prominent. The anterior pole of the composite dental lamina appeared to be composed by the fused anterior parts of the MPDL and the medial primary dental laminae (Fig. 4C).

In 12(12) embryos (101-125 mg wt.c.), the composite dental lamina increased (Fig. 4D). The sheet of basal cells became thicker

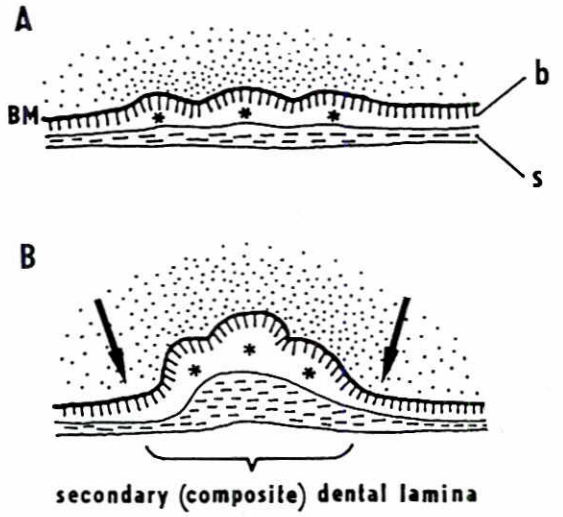

Fig. 2. Diagram depicting the odontogenic oral epithelium (A) bearing several primary dental laminae (asterisks) which give rise to the secondary (composite) dental lamina (B). *Arrow indicates the supposed centrifugal growth of the adjacent ectomesenchyme. Dotted area, ectomesenchyme; BM, basal membrane; b and s, basal and superficial layer of epithelial cells, respectively.*

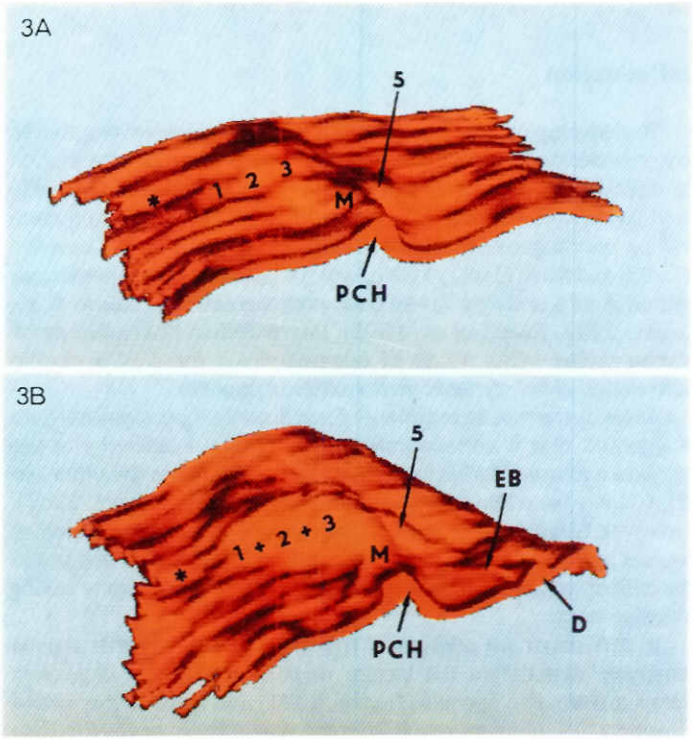

Fig. 3. Computer assisted 3-D-reconstructions *illustrating in postero-lateral view, the transformation of the area bearing the primary dental laminae in 12(12) embryo, wt.c. 76-100 mg* **(A)** *into a well formed composite incisor dental lamina in 12(24) embryo, wt.c. 101-125 mg* **(B)**. *Asterisk indicates the middle axis. PCH, the epithelium of the anterior margin of the primary choana; EB, epithelial band between the PDL 5 and the mesial diastemal dental anlage (D); 1, 2, 3, M and 5, the primary dental laminae 1, 2, 3, middle and 5, respectively.*

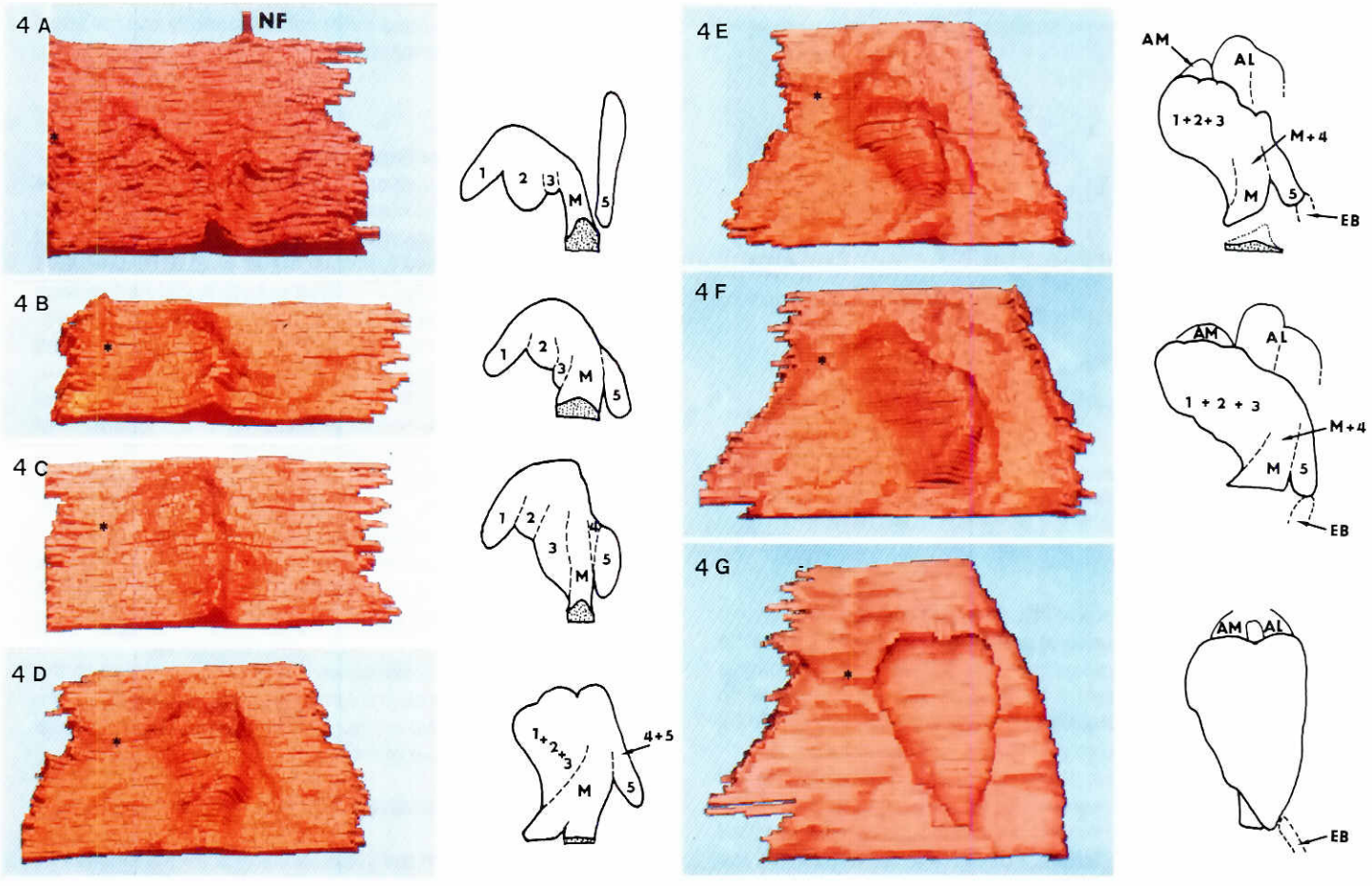

Fig. 4. Computer-assisted 3-D-reconstructions of serial sections of the oral epithelium involved in maxillary incisor formation and corresponding schematic interpretations. *Views of the mesenchymal face of the oral epithelium.* **(A)** *11(24) embryo, wt.c. 51-75 mg (embryo identical with Fig. 1).* **(B)** *11(24) embryo, wt.c. 51-75 mg.* **(C)** *12(12) embryo, wt.c. 76-100 mg (embryo identical with Fig. 3A).* **(D)** *12(12) embryo, wt.c. 101-125 mg.* **(E)** *12(24) embryo, wt.c. 101-125 mg (embryo identical with Fig. 3B).* **(F)** *12(24) embryo, wt.c. 126-150 mg (embryo identical with Fig. 7).* **(G)** *13(12) embryo, wt.c. 176-200 mg. (4A and B) depict the primary dental laminae which give rise to the composite dental lamina (4C,D,E,F) and finally to the early enamel organ (4G) of the right sided upper mouse incisor. Asterisks indicate the middle axis. The epithelium of the anterior margin of the primary choana is dotted. AM, the anteromedial projection; AL, the antero-lateral projection; 1, 2, 3, 4 and 5, the primary dental laminae 1, 2, 3, 4 and 5, respectively; M, the middle primary dental lamina; EB, the epithelial band extending between the PDL 5 and the mesial diastemal dental anlage; NF, the nasal fin. The variation of the epithelial thickness has been magnified mathematically using exponential coefficients 1.7 (4A), 1.5 (4B,C,D) and 1.3 (4E,F). In 11(24) embryos, the schematic contour lines of the medial primary dental laminae could be estimated only after comparison with the corresponding histological sections and with regards to 4C.*

and there was an increased accumulation of the flat cells (Fig. 6). With the exception of the posterior part of the PDL 3, the medial primary dental laminae were no longer distinguishable and formed a common epithelial thickening which joined the anterior part of the MPDL (Figs. 4D and 6).

The arrangement of the main part of the composite dental lamina did not differ significantly from the previous stage. The well developed lateral PDL 5 lay alongside the posterior part of the composite dental lamina. More anteriorly it decreased. The lateral PDL 4 was distinguishable as a part of the lateral slope of the composite dental lamina (Fig. 6).

In developmentally more advanced embryos, two anterior projections emerged from the composite dental lamina: the antero-medial projection represented the anterior continuation of the crest of the composite dental lamina, and the antero-lateral projection seemed to be formed by the anterior continuation of the lateral primary dental laminae (Fig. 6).

In 12(12) embryos (126-150 mg wt.c), the arrangement of the dental laminae did not differ significantly when compared with the embryos weighing 101-125 mg. The lateral PDL 5 was more voluminous and cell degeneration was sporadically seen inside the flat cell population.

In 12(24) embryos (101-125 mg and 126-150 mg wt.c.) further morpho-differentiation of the composite dental lamina was apparent (Figs. 3B, 4E,F, and 7). Its crest increased, tending to roll over the lateral parts and fusing with them. In this way, the anterior part of the lateral PDL seemed to be incorporated into the lateral slope of the composite dental lamina (Figs. 4F and 7).

At the anterior pole of the composite dental lamina, its crest became lower and did not fold laterally. As a result of this, the laterally situated part of the composite dental lamina was exposed giving rise to the antero-lateral projection (Fig. 4F). The lateral PDL

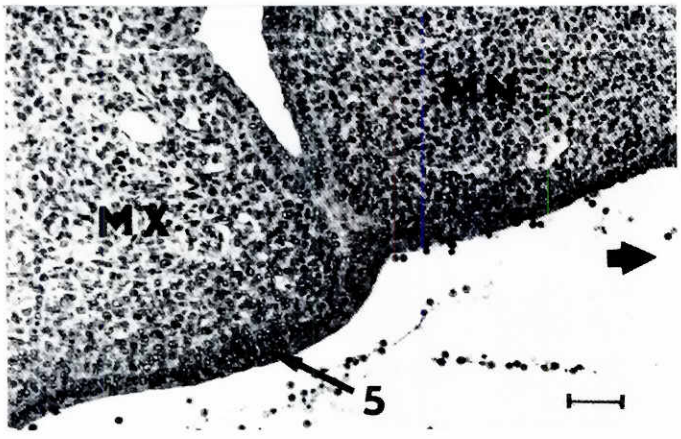

Fig. 5. Frontal section of the oral cavity of 12(12) embryo, wt.c. 76-100 mg. *Large arrow points medially. MX and MN, the maxillary and medial nasal outgrowth, respectively; 5, the lateral PDL 5. Bar, 50 μm.*

4, and perhaps even the lateral PDL 5, appeared to be engaged in the formation of the antero-lateral projection. The medial part of the composite dental lamina transformed into the antero-medial projection of the composite dental lamina; it was not possible to determine to what extent the MPDL and the medial primary dental laminae participated in these projections.

Two posterior projections of the composite dental lamina were observed: one of them, directed dorso-medially, seemed to correspond to the MPDL, the other directed dorso-laterally, represented the posterior part of the lateral PDL 5. The connection of the composite dental lamina and the primary choana was no longer apparent (Fig. 4E,F). In the embryos weighing 126-150 mg, signs of cell degeneration were sporadically seen inside the population of flat cells belonging to the PDL 5.

A very subtle epithelial band (Figs. 3B, and 4E,F) connected dorsally the posterior end of the lateral PDL 5, and the mesial diastemal dental anlage (Peterková *et al.*, 1993).

In the most advanced *12(24) embryos (151-175 mg wt.c.)*, the anterior part of the composite dental lamina was more voluminous than in 12(24) embryos of lower weight classes. The composite dental lamina tapered off gradually from the medial side in a dorsal direction. The posterior part of the lateral PDL 5 (see Fig. 4F) was no longer distinguishable, having been probably incorporated into the lateral part of the composite dental lamina.

Granular substances signalling the presence of degenerating cells (Kindaichi, 1980) were sporadically seen in the population of flat cells situated in the laterobasal part of the composite dental lamina.

In 13(12) embryos (Fig. 4G), the composite dental lamina acquired the morphology of an early enamel organ. The antero-medial and antero-lateral projections, the tapering of the posterior part from medial side as well as the splitting of the posterior end into 2 parts were observed.

In 13(24) to 15(24) embryos, there were both antero-medial and antero-lateral projections, which fused together posteriorly to form the solid anterior pole of the enamel organ. In the posterior direction, the incisor enamel organ tapered off. This narrowing seemed to result from the gradual individualization of the most medially situated parts of the composite incisor epithelial anlage. Each separate epithelial band extended posteriorly over a short distance, alongside the remaining part of the enamel organ (Fig. 8).

Discussion

Multiple origin of the maxillary incisor

The functional muroid incisor is supposed to correspond to the middle incisor of the general eutherian dental formula (I_3, C, P_4, M_3), while the other two are suggested to have been lost during muroid evolution (Hershkovitz, 1967). Strassburg *et al.* (1970) described 3 incisor epithelial thickenings indicated as I_1, I_2, I_3 situated on each of the medial nasal outgrowths in 11.5-day-old mouse embryos. According to these authors, only the middle anlage (I_2) persisted while the other two regressed at very early stages. Our data, however, did not support this conclusion; we found 6 epithelial anlagen (primary dental laminae) in each upper jaw quadrant of 11(24) embryos. The primary dental lamina (PDL 1) and the middle primary dental lamina (MPDL) appeared to correspond to anlage I_1 and I_2, respectively, in the figure provided by Strassburg *et al.* (1970); anlage I_3 has not been documented by these authors.

By their arrangement on histological sections, the primary dental laminae were comparable to the dental placodae described by Westergaard (1988) as the primordia of the first tooth generation in reptiles.

All the primary dental laminae we observed contributed to the formation of the definitive dental lamina of the mouse incisor. The epithelial component of the mouse incisor dental anlage is, therefore, a composite structure of multiple origin.

The incisor composite lamina originates from infolding of the epithelial sheet

It is often assumed that the initial invasion of dental lamina into the subadjacent ectomesenchyme is an active process resulting partially from differential proliferation of the odontogenic epithelial cells, even if locally increased mitotic activity has not been observed (Osman and Ruch, 1976). Orban (1928) found that in man the distance between the uppermost part of the dental anlage and the floor of the nose remained constant at each developmental stage. He excluded, therefore, an active ingrowth during tooth development; dental lamina and tooth germ development could result from the centrifugal growth of surrounding tissues. Moss-Salentijn (1982) also supported this opinion by quantitative evaluation of the distances between dental and nondental structures in rat and cat embryos and fetuses. We also conclude that the centrifugal growth of the adjacent mesenchyme is involved in the composite lamina formation (Fig. 2).

During dental lamina development in mice, Pourtois (1961) described the origin of the flat superficial cell layer and the elongation of basal cells, and then, during incisor epithelial bud formation, the appearance of an inflection of the basal epithelial cell layer against mesenchyme and the sliding of the superficial cells into the forming groove. Our results confirm in principle Pourtois' description. We found, however, that the prospective odontogenic epithelial zone was not smooth but bore several primary dental laminae which together are all involved in the epithelial folding (Figs. 2 and 3).

The maxillary outgrowth contributes to the formation of the incisor composite dental lamina

According to the description of primary palate formation in man (Warbrick, 1960) and in mouse (Pourtois, 1972), in 11-day-old

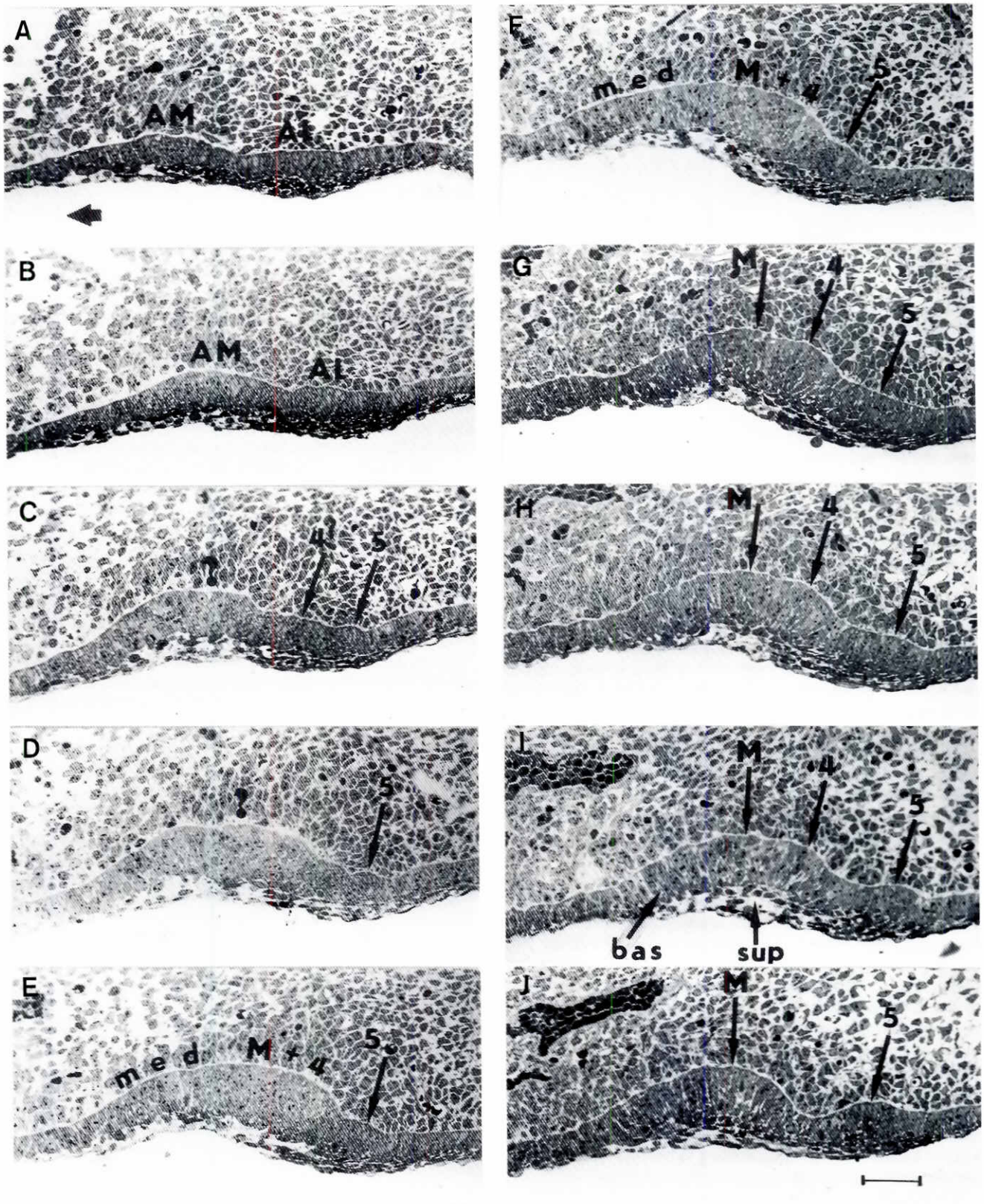

Fig. 6. Formation of the composite incisor dental lamina documented by 10 representative frontal sections (antero-posterior sequence) in 12(12) embryo, wt.c. 101-125 mg. *Large arrow points medially, narrow arrows indicate the primary dental laminae. M, the middle PDL; 4 and 5, the primary dental laminae 4 and 5, respectively; med, epithelial thickening representing fused medial primary dental laminae 1, 2 and 3. AM and AL, the antero-medial and antero-lateral projection, respectively; bas, basal layer of epithelial cells; sup, superficial layer of epithelial cells. Bar, 50 μm.*

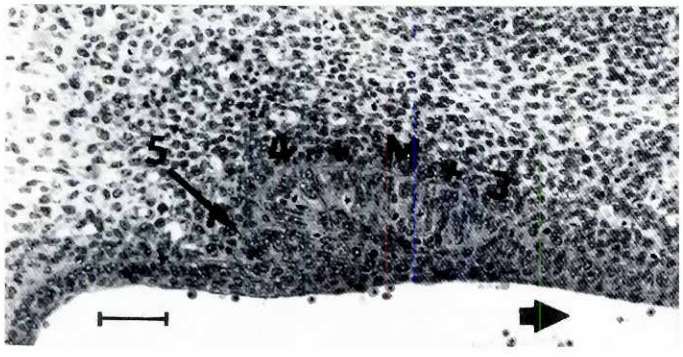

Fig. 7. Frontal section of the incisor anlage in 12(24) embryo wt.c. 126-150 mg documenting the incorporation of the lateral PDL 5 into the composite dental lamina. *Large arrow points medially; 5, the primary dental lamina 5; 4 + M + 3, fused primary dental lamina 4, middle and 3. Bar, 50 μm.*

embryos, the primary choana and the epithelium attached to its anterior margin can be considered as the reference structure indicating the place of previous fusion between the medial nasal and maxillary outgrowths. The middle primary dental lamina was located directly anterior to the epithelium lining the anterior margin of the primary choana (Fig. 4A-C). As the lateral primary dental lamina 5 was found lateral to this place (Fig. 5), the maxillary outgrowth also appeared to participate in the formation of the incisor composite dental lamina. The contribution of maxillary outgrowth to incisor formation is not surprising. Among therian ancestors of recent mammals there were animals possessing the most lateral upper incisor situated in the anterior part of the maxilla, in front of caninus (Kermarck and Musset, cited by Ziegler, 1971). The lateral incisor in man (I_2) appears to be a composite structure involving material of two facial outgrowths (Politzer and Weizenberg, 1954; Ooë, 1957; Böhn, 1963). This possibility is supported by the existence of an incisive suture ending in the lingual lamina of the alveolus of the upper lateral incisor in two thirds of a sample of 50 human fetuses investigated by Bollobás (1984).

Asymmetry of the mouse incisor enamel distribution

One of the typical features of the mouse incisor is the absence of enamel on its lingual side. Both the labial and lingual parts of the enamel organ might differ not only as far as final structure and function are concerned (Beersten and Niehof, 1986; Amar *et al.*, 1989; Nso *et al.*, 1992), but also at the level of their developmental origin. The upper incisor enamel organ proved to be a composite structure originating from several primary dental laminae whose contributions appeared to differ, along the antero-posterior axis of the incisor epithelial anlage (Fig. 4). We suggest that the cells of specific parts of the incisor enamel organ differ both in developmental origin and also as far as the history of tissue-interactions is concerned. In this way, the different developmental potencies of the parts of the incisor enamel organ leading to the final asymmetry of enamel distribution could be hypothetically explained.

Comparative embryological and phylogenetic aspects of incisor development

The unreduced number of 5 upper and 4 lower incisors, characteristic for common fossil ancestors of recent placentals and marsupials, now exists only in some marsupials (Ziegler, 1971). According to the pattern of their functional dentition, marsupials can be divided into the more conservative polyprotodonts with 5 upper and 4 lower incisors, and the caenodestoids and diprotodonts, whose number of incisors has been reduced to 1-4 (Peyer, 1963). Development of 5 upper functional incisors in Didelphidae has been documented in 3-D models by Röse (1892a,b). Despite the reduced number of functional incisors in some marsupial families, the number of initial incisor anlagen may be higher: e.g. 5-7 incisor tooth germs develop in each upper jaw quadrant in Phalangeroidae, where finally only 3 functional upper incisors are present (Berkovitz, 1968). Difficulties arise, however, as far as the classification of both the individual tooth germs and the functional teeth into appropriate tooth generations is concerned (Röse, 1892a,b; Woodward, 1896; Wilson and Hill, 1897; Berkovitz, 1968; Fosse, 1969; McKenna, 1975).

During evolution, the number of teeth in recent placentals has been reduced (Ziegler, 1971). According to Wood (1962), the reduction of tooth number, the lengthening of incisors and the reduction of their enamel cap preceded the first appearance of Rodentia (family Paramyidae) in the late Paleocene. Recent rodents have only 1 functional incisor in each jaw quadrant.

Beside germs of functional incisors, further rudimental incisor tooth anlagen belonging to the same tooth generation have been reported only sporadically in recent placentals: Leche (1893) observed an abortive formation of the fourth incisor in Soricidae, although this has not been confirmed by later investigators (Woodward, 1896; Kindahl, 1959). Freund (1892) found one, and Woodward (1894) suggested the existence of two rudimental anlagen of the upper incisors in Squirrel.

We found six epithelial anlagen (primary dental laminae) in the anterior part of the mouse upper jaw quadrant, and all of them contributed to the early formation of the epithelial anlage of the upper incisor. The following hypothesis represents one possible

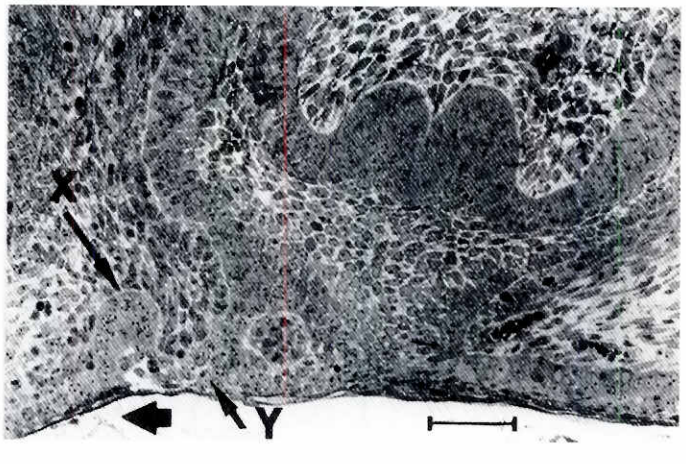

Fig. 8. Frontal section of 14(24) embryo, wt.c. 626-650 mg demonstrating the tapering of the posterior part of the upper incisor enamel organ due to the gradual separation of the epithelial band X and Y, (indicated by narrow arrows) from its medial slope. *Large arrow points medially. Bar, 50 μm.*

explanation of our finding in mouse embryos: five primary dental laminae (MPDL and PDL 1-4) might correspond to 5 upper incisors of early mammals, the most laterally situated primary dental lamina (PDL 5) could reflect the maxillary contribution to the most lateral incisor.

Heterochrony, defined as «phyletic change in the timing of development such that features of ancestors shift to earlier or later stages in the ontogeny of descendants» (Gould, 1992) appears to be one of the most promising concepts when ontogenetic and phylogenetic aspects are united (De Beer, 1940; Gould, 1977, 1992; Alberch *et al.*, 1979; McKinney, 1988). Rearranging of ancestral structures can lead to apparent novelty. From this point of view, heterochronic changes in differential growth of dental and interdental tissues in the upper incisor domain in mouse could contribute to close juxtaposition and to integrated evolution of the «repeated» tooth primordia.

Understanding of odontogenesis implies experimental embryology and genetic, molecular and phyletic approaches. However the interpretation of all such investigations requires the previous, detailed, knowledge of the three-dimensional, dynamic, morphology.

Materials and Methods

ICR mice were mated overnight and the day of vaginal plug was designated as day 0 of pregnancy. The embryos were harvested either at 12 noon or 12 midnight on days 12-15 and at 12 midnight on day 11. As morphological criteria for embryo staging according to Gruneberg (1943) and Theiler (1972) have proved to be too crude for detailed studies of early odontogenesis (Peterková *et al.*, 1993), the weight of the embryos was used as an additional criterion beside their chronological age. At each stage 11(24), 12(12), 12(24)... 15(24), the embryos were weighed and distributed into 25 mg weight classes (wt.c.).

Histological study

Paraffin sections

The embryos were fixed in Bouin-Holland fluid. At least three heads from each weight class of stages 11(24)-13(12) and 1-2 heads from each weight class of stages 13(24)-15(24) were embedded in paraffin and series of frontal 5 µm or 7 µm serial sections, stained with hematoxylin-eosin, were prepared. In total, 75 series were analyzed.

Semi-thin sections

One embryo of the median weight class of each stage 12(12)-15(24) was used. The upper jaw was dissected after glutaraldehyde (5% glutaraldehyde in phosphate buffer pH 7.5) fixation for 1.5 h. After washing in phosphate buffer (pH 7.5), the head fragments were postfixed for 1 h in 2% OsO_4 in phosphate buffer and dehydrated through a graded series of ethanol solutions (with 1% uranylacetate in 100% ethanol) and embedded in Durcupane-Epon medium, polymerized at 60°C for 3 days. 1 µm thin sections were stained with 0.1 toluidine blue solution at 45°C.

Three-dimensional reconstructions

Serial drawings (magnification 240x for the 11(24)-12(12) embryos, and 195x for 12(24)-13(12) embryos) of the oral epithelial layer of the right side of developing premaxilla and adjacent maxilla were made under a Wild-Leitz Orthoplan microscope equipped with a drawing chamber. Eight selected series of the 5 µm sections were used.

The digitalization of the serial drawings was achieved by means of a Hamamatsu C2400 camera connected to a digital imaging system (series 151 Imaging Technology). The position of the middle axis, the flexure of the vestibulum oris and the configuration of the oral surface of the epithelium allowed superimposition of the successive drawings. Correlation of successive images was performed by using a real time superimposition method (Olivo *et al.*, 1990).

A specific software module based on edge detection was developed in order to be able to magnify in parallel the variation of thickness of the oral epithelium by a linear or exponential function.

Three-dimensional images were made using a volume rendering software program (Sun Voxel Sun Microsystems).

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