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Contribution of 3-D computer-assisted reconstructions to the study of the initial steps of mouse odontogenesis

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ABSTRACT The specific arrangement of mouse dentition in each dental quadrant (1-0-0-3) is supposed to result from the initiation of two independent dental laminae – one for the incisor and one for the three molars. In order to verify whether the adult mouse dental pattern really corresponds to the initial patterning, an analysis of development of the mouse antemolar part of the upper dental quadrant was performed in 10-13 day embryos using histological sections and computer-assisted 3-D reconstructions. Six primary dental laminae contributed to the formation of the upper incisor anlage, which is, therefore, a structure of multiple origin. In contrast to the lower diastema, where only a low epithelial band extended mesially from the first lower molar in 12-13 day embryos, in the upper diastema a dental lamina existed interconnecting transiently the incisor and molar anlagen and giving rise to 3 distinct epithelial rudiments. The rudiments exhibited growth retardation and regressed after reaching a maximum at the bud stage. Our results showed a discrepancy between the embryonic and adult dental patterns in the mouse upper jaw. The specific arrangement of the mouse dentition implied a reduction of the embryonic dental anlagen, which was achieved either by their integration into the one incisor primordium or regression in the prospective diastema. Odontogenesis in the mouse upper jaw provides a model of hypodontia of evolutionary origin, which can be employed in molecular studies of the control mechanisms of initiation, spatial organization and specific morphogenesis of teeth.

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

Introduction

Mouse odontogenesis is the most frequently used model in studies of the control mechanisms of tooth development. However, since mouse dentition exhibits high functional-morphological specialization, it could be objected that this system is not the best for studies of the general principles of tooth development (see also Westergaard, 1986). Indeed, the number of antemolar teeth has been strongly reduced and the characteristic incisor developed (Fig. 1A) during rodent evolution (Wood, 1962; Hershkovitz, 1967). Among rodents, muroids exhibit the highest reduction of tooth number (Grassé and Dekeyser, 1955). In comparison with the general dental formula of eutherian mammals, which includes in each tooth quadrant three incisors, one canine, four premolars and three molars, in the mouse only one, huge and permanently growing incisor occurs, which is separated from a group of three molars by a large diastema occupying the place of missing antemolar teeth.

The mouse adult dental pattern is generally supposed to be identical with the embryonic dental pattern resulting from initiation of two independent dental laminae — one for the incisor and one for the group of three molars. Our previous data (Peterková *et al.*, 1993a,b) suggested, however, that traces of the "lost" antemolar teeth may occur in the upper jaw of mouse embryos.

In order to determine the relationship between the adult and embryonic tooth patterns in mice, an analysis of development of the morphologically specific part of dental quadrant (i.e. the incisor and diastema domain) was performed in the upper jaws of 10-13 day embryos using frontal histological sections and computer assisted 3-D reconstructions. The findings showed a discrepancy between the embryonic and adult dental patterns in the mouse. Establishment of the characteristic arrangement of mouse upper dentition included reduction of embryonic tooth anlagen at specific positions. These data demonstrate that mouse odontogenesis represents a powerful tool for investigating general mechanisms involved in patterning, initiation and tooth class specific morphogenesis.

Abbreviations used in this paper: 3-D, three dimensional; wtc., weight class; D1, D2 and D3, first, second and third diastemal dental rudiment.

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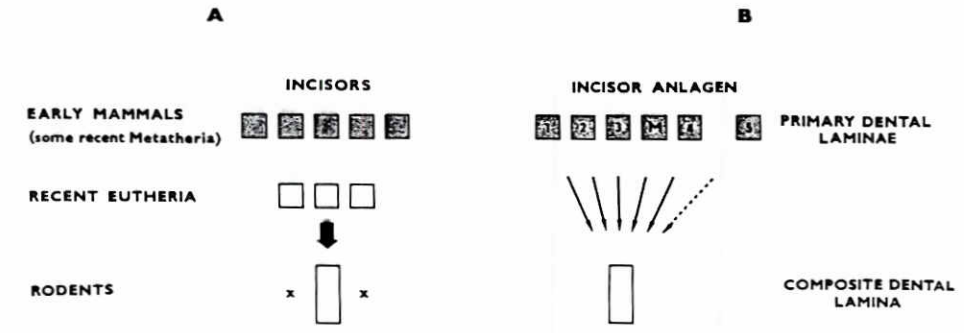


Fig. 1. Schematic representation of upper rodent incisor development: (A) *supposed phylogenic reduction of number of the upper incisors from maximally 5 in mammalian ancestors to 3 incisors found in recent eutherians (Ziegler, 1971). The rodent incisor is assumed to correspond to the second incisor of the general dental formula of placental mammals (Hershkovitz, 1967; Strassburg et al., 1970).* **(B)** *Ontogenic reduction of the primary dental laminae 1-5 and M (middle) by their integration into the only upper incisor anlage in mouse embryos.*

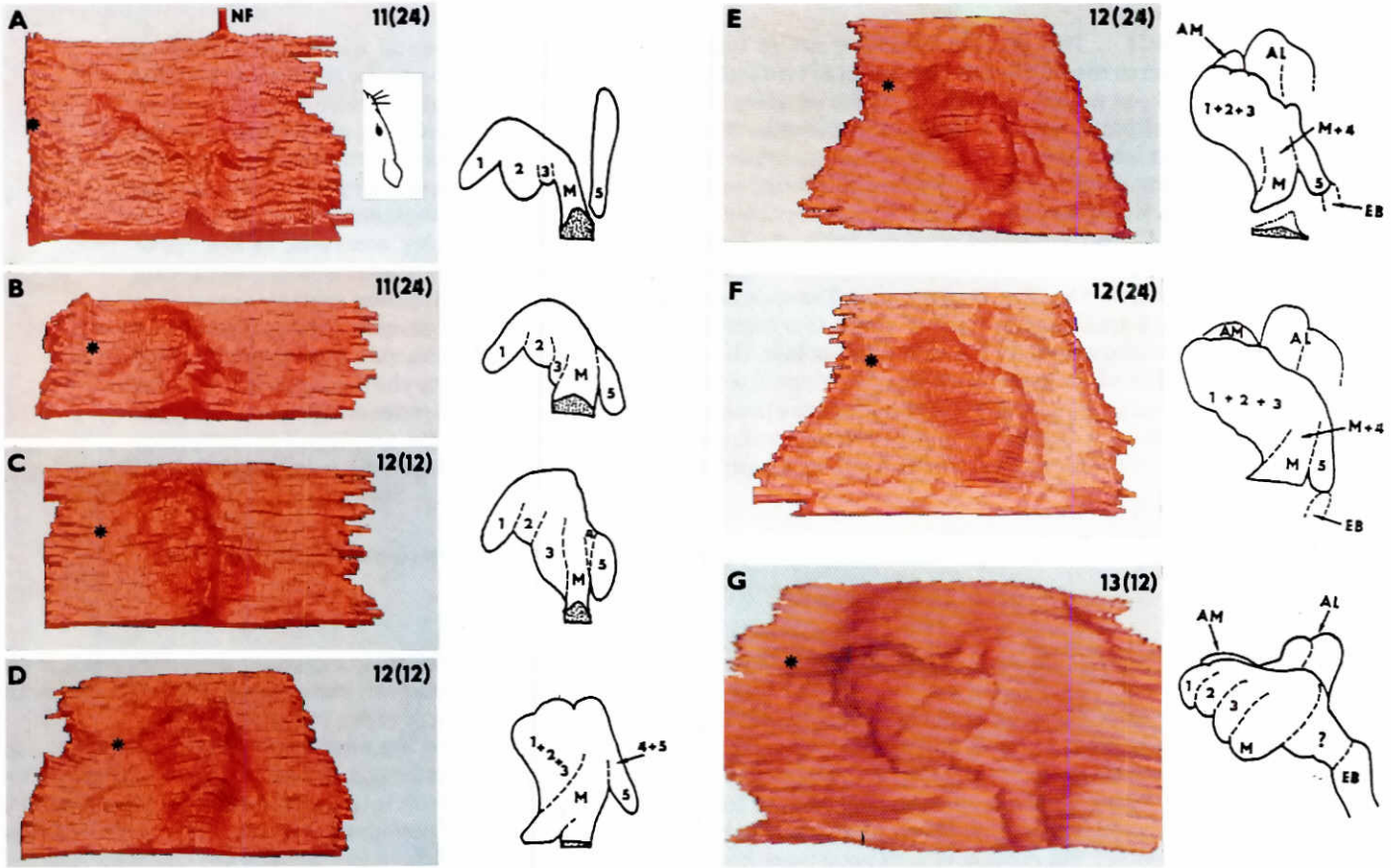


Fig. 2. ICR mouse embryos were harvested at 12 and 24 h within days 10-13 (vag. plug= day 0), i.e. at chronological stages 10(12), 11(12), 12(12), 13(12) and 10(24), 11(24), 12(24), 13(24), respectively. *The embryos at each chronological stage were further distributed into 25-mg weight classes (wtc.) for the purpose of a more detailed analysis of relatively fast developmental processes. Details concerning the material and methods have been described before (Peterková et al., 1993b). Computer-assisted 3-D reconstructions of serial sections of the oral epithelium in the mouse upper right incisor region and corresponding schematic interpretations. Views on the mesenchymal surface of the epithelium.* **(A)** *11(24) embryo, wtc. 51-75 mg;* **(B)** *11(24) embryo, wtc. 76-100 mg;* **(C)** *12(12)embryo, wtc. 76-100 mg;* **(D)** *12(12) embryo, wtc. 101-125 mg;* **(E)** *12(24) embryo, wtc. 101-125 mg;* **(F)** *12(24) embryo, wtc. 126-150 mg;* **(G)** *13(12) embryo, wtc. 126-150 mg.* **(A and B)** *depict the primary dental laminae which give rise to the composite dental lamina* **(C,D,E,F)** *and finally to the epithelial bud* **(G)**. *Asterisks indicate the middle axis. AM and AL, the anteromedial and anterolateral projection, respectively; 1,2,3,4,5 and M, the primary dental laminae; EB, the epithelial band extending between the primary dental lamina 5 and the mesial diastemal dental anlage; NF, the nasal fin. The epithelium of the anterior margin of the primary choana is dotted. The question mark indicates the supposed distal end of the primary dental lamina 5.*

Results

The upper incisor epithelial anlage in 3-D reconstructions

In embryos of day 11, five distinct epithelial swellings — primary dental laminae — protruded against the mesenchyme (Fig. 2A). It was possible to identify these structures, whose final number was 6, during further development (Fig. 2B,C). In the course of establishment of the incisor epithelial anlage, the whole epithelial field bearing the primary dental laminae infolded into the mesenchyme (compare Fig. 2A,B and 2C-E). In this way, the primary dental

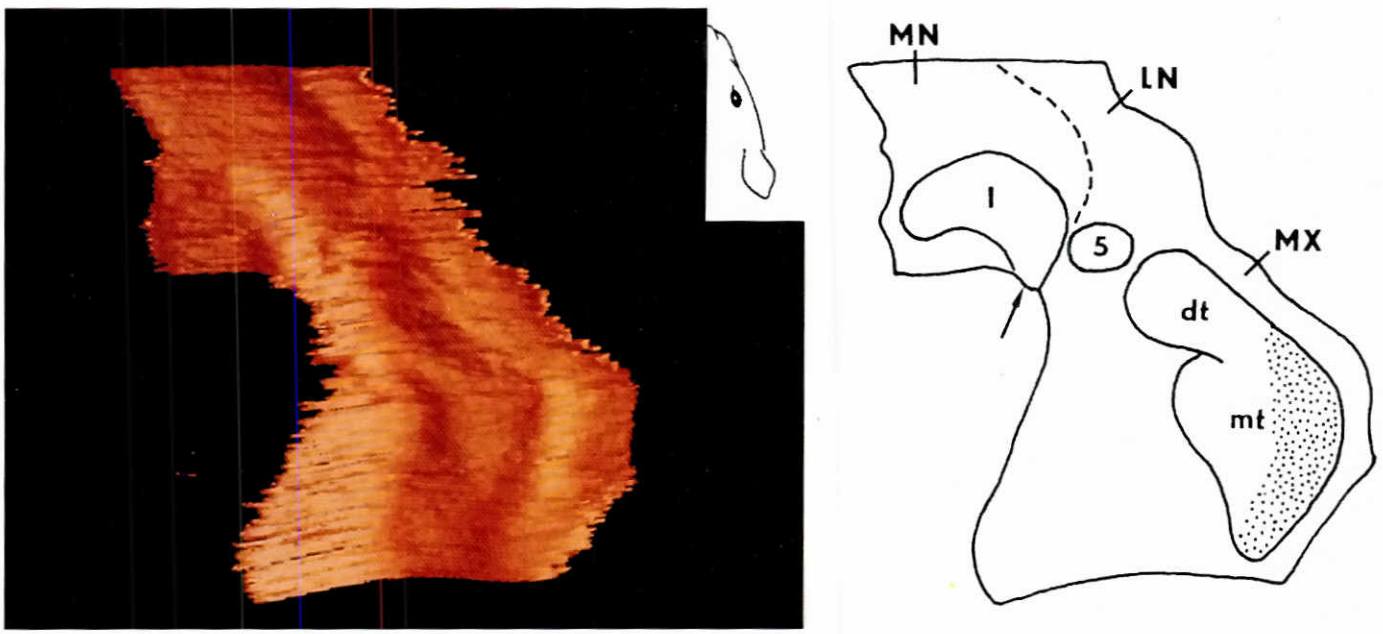


Fig. 3. Computer-assisted 3-D reconstruction of the right upper jaw oral epithelium and its schematic interpretation in the 11(24) mouse embryo (wtc. 76-100 mg). *View on the mesenchymal surface of the epithelium. I, incisor domain; dt and mt, epithelial thickening in the prospective diastema and molar region, respectively. The supposed molar dental epithelium is dotted. The primary dental lamina 5 (5) is situated laterally to the assumed place of fusion (dashed line) between the medial nasal (MN) and lateral nasal (LN) or maxillary (MX) facial processes. The arrow indicates position of the primary choana.*

laminae contributed to the formation of the incisor dental lamina. During the early bud stage, a segmentation, reflecting the existence of several subunits, was still very apparent (Fig. 2G). It was not possible to determine to what extent the epithelial material situated laterally to the incisor bud corresponds to the distal end of the primary dental lamina 5. This material, however, contributed to the incisor bud in course of its further growth on day 13. Together these data demonstrate that the upper mouse incisor represents a complex structure of multiple origin (Fig. 1B).

The upper diastema epithelium in 3-D reconstructions

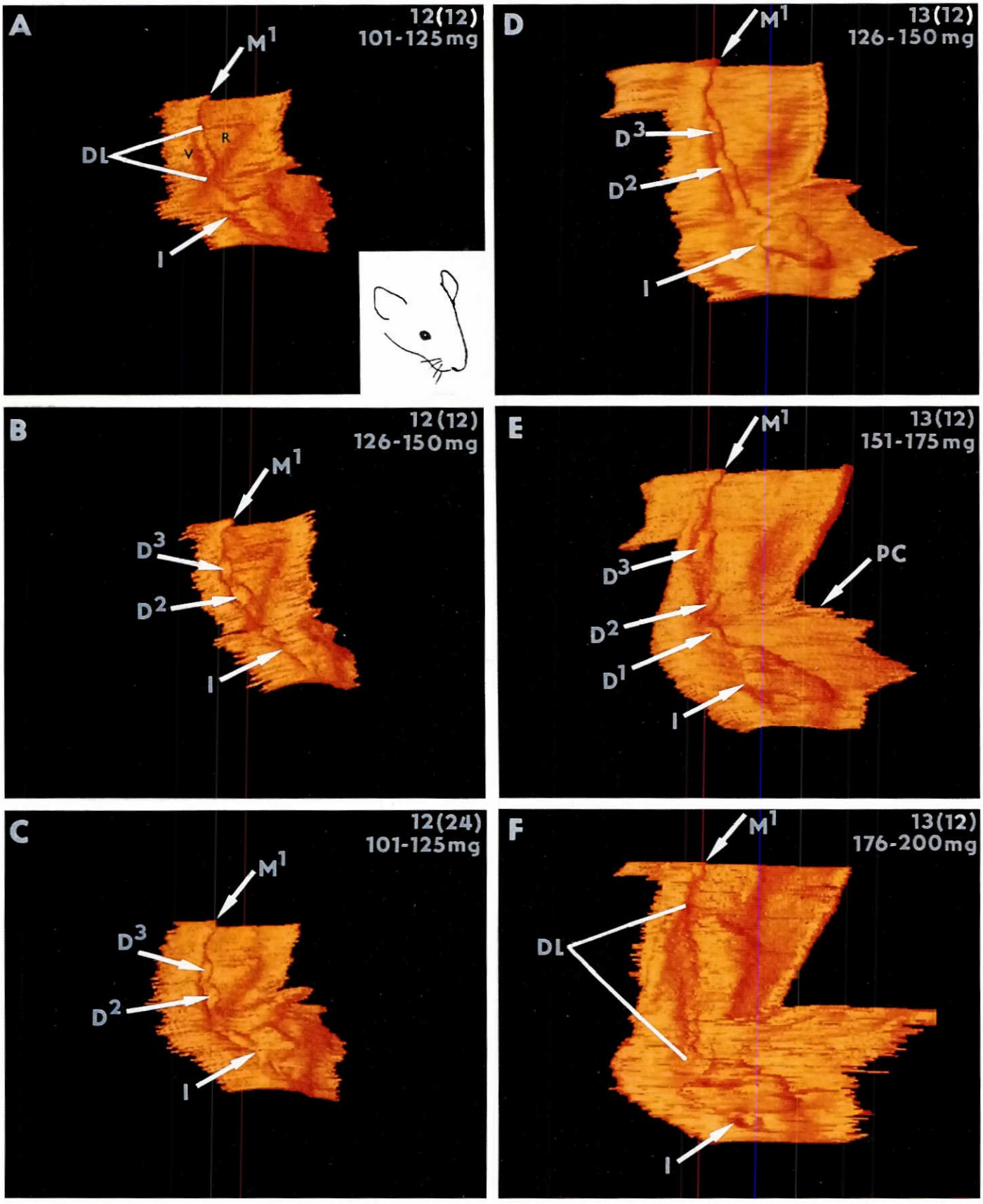
Initially, a continuous epithelial thickening representing the common anlage of dental lamina, vestibular lamina and palatal rugae (Peterková, 1985) was found on the maxillary oral surface including both the prospective diastema and molar region (Fig. 3, compare with Fig. 6). The maxillary epithelial thickening was separated by a gap from the incisor domain. Later on, the vestibular lamina (lip-furrow band), the diastemal dental lamina and the anlage of the palatal rugae individualized (Fig. 4A, compare with Fig. 7). The mesial pole of the diastemal dental lamina was separated by a gap from the incisor composite dental anlage. Distally, the diastemal dental and vestibular laminae converged and fused with the mesial slope of the molar epithelial anlage.

In more advanced embryos, two distinct epithelial buds (D2, D3) were apparent in front of the first molar. Their size was, however, conspicuously smaller in comparison with the incisor (Fig. 4B,C) or molar anlage (compare with Figs. 5 and 7). The spatial relationships between the diastemal dental epithelium and adjacent oral structures did not change in comparison with the previous stage. During subsequent stages (Fig. 4D), the D2 and D3 epithelial buds decreased meanwhile the diastemal dental lamina was continuous mesially with the distobuccal extension of the composite incisor anlage (compare with Fig. 2) and distally with the molar epithelium. In this way, a continuous epithelial ridge along the whole upper jaw quadrant was transiently present, bearing both the persisting (incisor, molars) and rudimental (diastemal) dental primordia.

During day 13, the diastemal dental lamina was disrupted between D2 and D3. At the place of the previous interconnection between the diastemal and incisor dental epithelium, the most mesial epithelial rudiment (D1) became apparent laterally to the primary choana (Figs. 4E and 5, compare with Fig. 8). From this stage, however, the diastemal structures quickly disintegrated and only poor remnants were seen in the more advanced embryos (Fig. 4F).

The prospective diastema in histological sections

Initially, an epithelial thickening was present in both, the upper diastema and molar regions (Fig. 6A-C and D-F, compare with Fig. 3). Its configuration and position on the maxillary oral surface differed in frontal sections, when diastema and molar regions were compared: in the diastema, the thickened epithelium lacked an apparent top. At the assumed level of the prospective D2 anlage, the thickening was situated rather in the medial half of the maxillary oral surface, which exhibited a shallow inflection (Fig. 6A,D). In the distal direction, the maxillary oral surface as well as the epithelial thickening enlarged and its center was situated at the assumed D3 level approximately in the middle (day 10) or palatally to the middle (day 11) of the maxillary oral surface, decreasing gradually in both the palatal and buccal directions (Fig. 6B,E). In the molar region, the epithelial thickening was characterized by a suggested top situated in the buccal half of the maxillary oral surface at the level of the lip (Fig. 6C,F) or close to the cheek furrow (indicating place of interconnection between the maxillary and mandibular facial outgrowths). In the area adjacent to the maxillary oral epithelium,


A
12(12)
101-125mg
M1
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V
R
I
B
12(12)
126-150mg
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D3
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I
C
12(24)
101-125mg
M1
D3
D2
I
D
13(12)
126-150mg
M1
D3
D2
I
E
13(12)
151-175mg
M1
D3
PC
D2
D1
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F
13(12)
176-200mg
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the mesenchymal cells were condensed (Fig. 6). Laterally to the primary choana, an area of the thick epithelium (corresponding to the incisor primary dental lamina 5) was found on the palatal edge of the maxillary facial outgrowth (compare with Fig. 3).

At the end of day 11, shallow depressions appeared in the mesenchymal surface of the diastemal epithelium (Fig. 7A,B). These depressions deepened during day 12 separating the epithelium of the palatal ruga, dental lamina and vestibular lamina (Fig. 7D,E and G,H). The diastemal dental lamina was, however, conspicuously smaller in comparison with the molar. At the same time, the long axes of nuclei of the adjacent mesenchymal cells became arranged either uniformly above the ruga epithelium or rather parallel and perpendicularly to the basement membrane of the dental and lip furrow epithelium, respectively (Fig. 7 G,H). As a result of the diastemal dental lamina differentiation, the distinct primordia of D2 and D3 appeared and reached maximum size during day 12 (Fig. 7G,H). In these embryos, a reversal of the hitherto progressive development of the D2 and D3 primordia occurred with a significant amount of dying cells being observed inside the epithelium signalling the start of the regressive phase.

In developmentally less advanced day 13 embryos, the D1 diastemal anlage was transiently detected (Fig. 8). In developmentally more advanced day 13 embryos, the diastemal buds were no longer apparent and the dental lamina disintegrated and finally disappeared. Only its most distal part was preserved and, as a low epithelial band, projected anteriorly from the mesial slope of the first molar anlage (Fig. 9).

A previous preliminary histological investigation of the prospective mandibular diastema revealed the presence of a low epithelial band extending mesially from the first molar anlage in 12-13 day embryos (Fig. 9). The differentiation of tooth buds as well as signs of degeneration were not observed there.

Discussion

Our data has demonstrated a discrepancy between embryonic and adult dental patterns in mouse.

In the upper incisor region, 6 primary dental laminae existed contributing to the formation of the only one rodent incisor anlage, which is, therefore, a complex structure of multiple origin. Five more medially situated primary dental laminae (Figs. 1B, 2 and 10) could hypothetically correspond to 5 incisors found in mammalian ancestors (Ziegler, 1971) and some recent marsupials (Peyer, 1968), (Fig. 1A). The most laterally situated primary dental lamina 5 (Figs. 1B, 2 and 3) might represent a maxillary contribution to incisor development (Peterková *et al.*, 1993b). The participation of the maxillary facial outgrowth in the lateral incisor development has been reported in man (Politzer and Weizenberg, 1954; Ooë, 1957; Böhn, 1963; Schwartz, 1982).

In the upper diastema, a dental lamina existed interconnecting transiently the incisor and molar anlagen and giving rise to 3 distinct, transitory, dental primordia (D1, D2, D3). Their size, however, was always conspicuously smaller in comparison with the anlagen of the persisting teeth (Figs. 4-7). The growth retardation culminated with disappearance of the diastemal bud epithelium. In the mandible, the diastemal dental lamina remained inconspicuous in comparison with the upper one and no differentiation of distinct tooth primordia was apparent (Fig. 9). In mouse embryos, the two more distal diastemal tooth primordia (D2, D3) situated in front of the upper first molar and the presence of a very low dental lamina extending mesially from the lower first molar might correspond to two upper and one lower premolars found in the fossil rodents Paramyidae (Viret, 1955; Wood, 1962) and in some recent rodents (squirrels), (Grassé and Dekeyser, 1955). This may reflect the general trend towards premolar extinction among rodents — always more advanced in the lower jaw (Luckett, 1985). On the basis of our data presented here, we can only speculate as to whether the D1 epithelial rudiment, located at the level of the primary choana (Figs. 4,5 and 8) might correspond to the canine or other premolar of rodent ancestors.

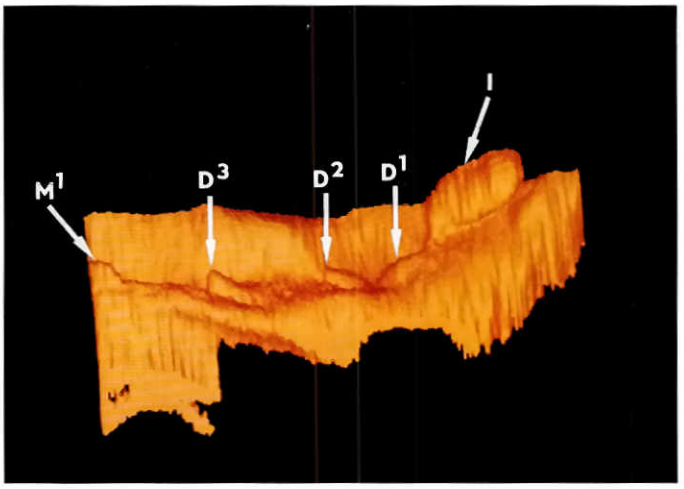

Fig. 5. Computer-assisted 3-D reconstruction of the oral epithelium covering the antemolar part of the right upper jaw in the 13(12) mouse embryo, wtc. 151-175 mg (lateral view on the mesenchymal surface of the epithelium). *For explanation of abbreviations see Fig. 4.*

Our results have shown that the highly specialized mouse dentition does not result from a simple ontogenic disclosure of only one incisor and three molar anlagen in each upper jaw quadrant. The mouse adult dental pattern originates from secondary reduction of the embryonic (developmental) dental pattern, which also includes dental anlagen of supposed ancestral teeth. A reduction of these anlagen was achieved by two mechanisms: by their integration into the single dental primordium in the incisor domain and by their disappearance in the prospective diastema (Fig. 10).

Phylogenetic changes in dentition, correlated with functional adaptation, raise important questions concerning the evolution of developmental decisions and the mechanisms used to put them into practice. The prenatal development of "abnormal" teeth can be interpreted as an intermediate stage in the evolutionary loss of teeth at specific positions (Moss-Salentijn, 1978; Luckett, 1985). The total elimination of the vestigial structures can be expected during future evolution, via elimination of the appropriate developmental programme to "conserve developmental energy" (Maderson, 1975).

Fig. 4. Computer-assisted 3-D reconstructions of the oral epithelium covering the antemolar part of the right upper jaw (anterolateral view on the mesenchymal surface of the epithelium). *The chronological age and wtc. of the embryos is introduced in the right upper corner. I, the incisor composite anlage; DL, the diastemal dental lamina; D1, D2, and D3, the first, second and third diastemal dental anlage, respectively; M1, the mesial slope of the first molar anlage; R, palatal rugae anlage; V, vestibular lamina; PC, anterior margin of the primary choana.*

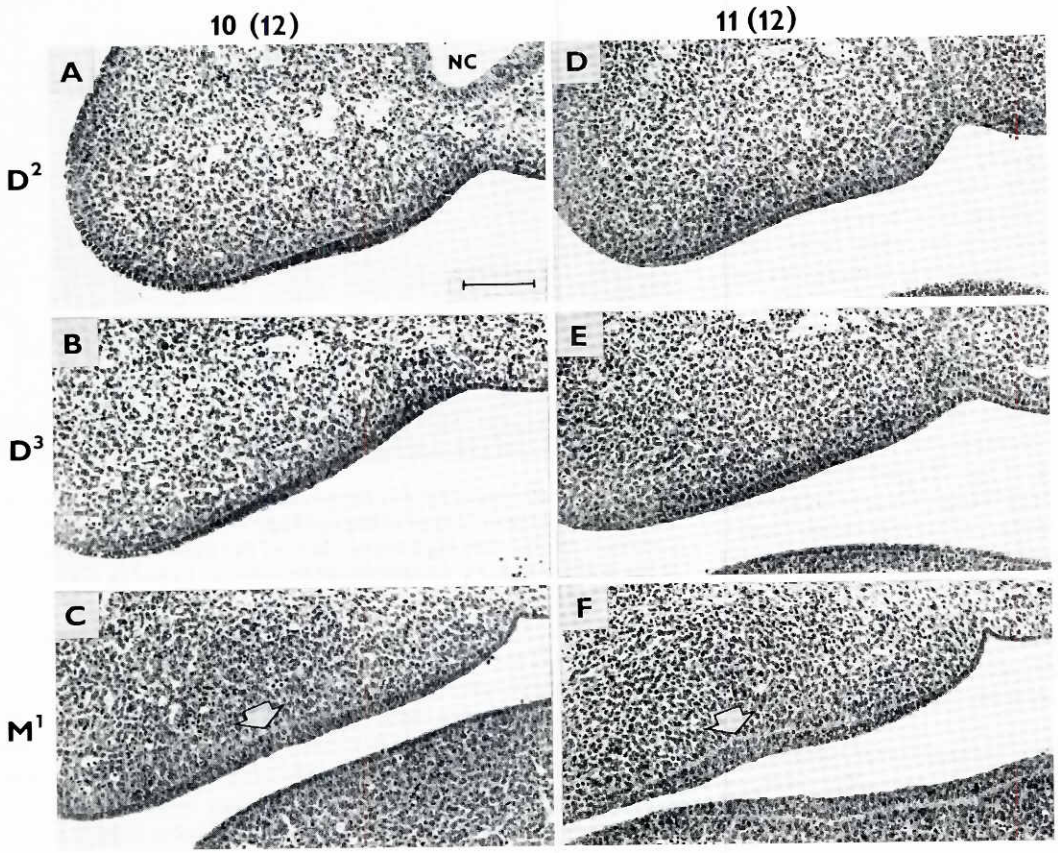

Fig. 6. Frontal histological sections demonstrating the maxillary oral epithelial thickening *at the assumed level of the prospective second and third diastemal dental rudiment (D2 and D3, respectively) and the anterior part of the first molar anlage (M1) at stages 10 (12) - embryo from wtc. 26-50 mg, and 11(12) - embryo from wtc. 51-75 mg. NC, nasal cavity. Arrow indicates a top of the epithelial thickening in the molar region. Bar, 100 μm.*

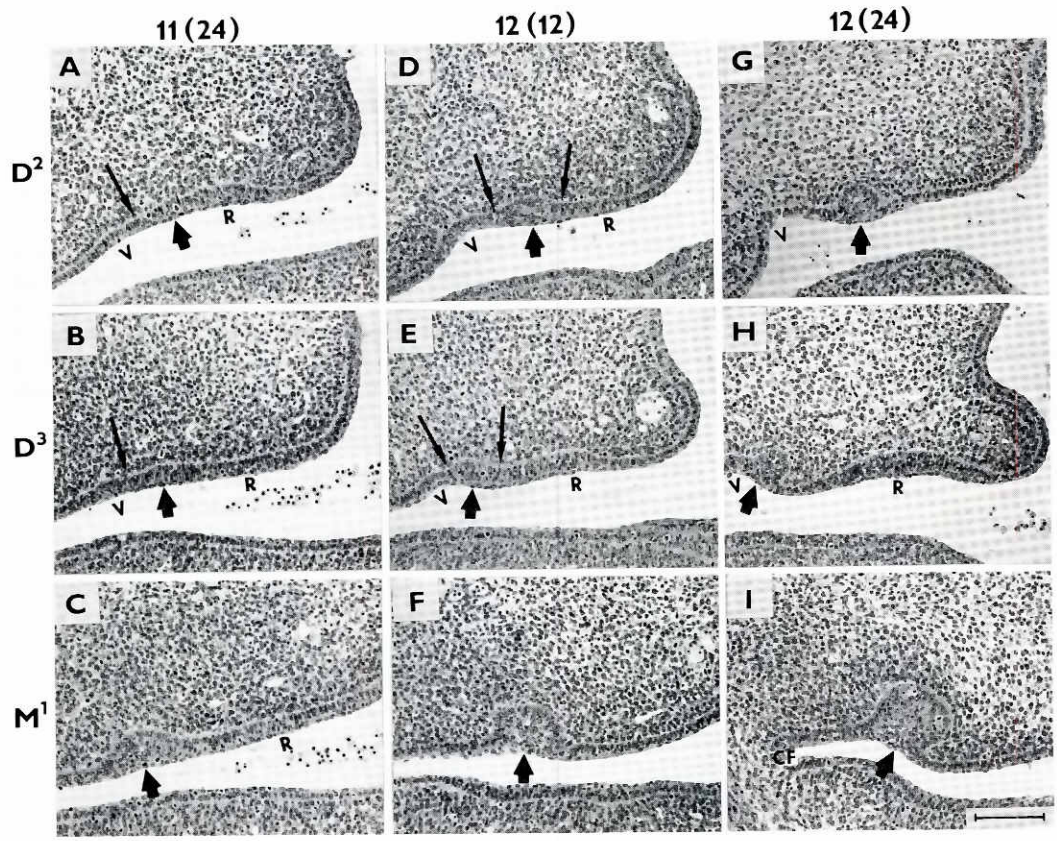

Fig. 7. Frontal histological sections demonstrating differentiation of the maxillary oral epithelial thickening *at the level of the second and third diastemal dental rudiment (D2 and D3, respectively) and the anterior part of the first molar anlage (M1) at stages 11(24) - embryo from wtc. 76-100 mg; 12(12) - embryo from wtc. 76-100 mg, and 12(24) - embryo from wtc. 101-125 mg. V, vestibular lamina; R, epithelium of the palatal ruga; CF, cheek furrow. Large arrow indicates position of the dental epithelial anlage. Slim arrow points to depression separating the diastemal dental rudiment from the vestibular lamina or ruga epithelium. Bar, 100 μm.*

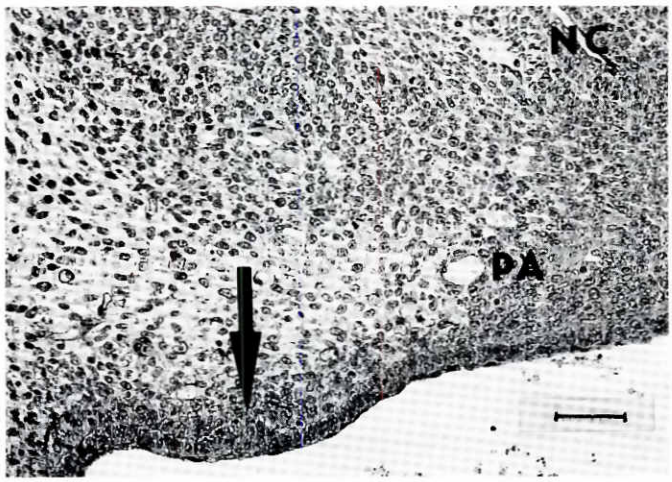

Fig. 8. Frontal histological section of the first upper diastemal dental anlage D1 (arrow) in the embryo 13(12), wtc. 151-175 mg. *NC, nasal cavity; PA, palatal artery. Bar, 50 μm.*

The transitory existence of an ancestral dental pattern in mouse embryos could be explained in terms of the onto-phylogenetic concept of heterochrony (De Beer, 1940; Gould, 1977; Alberch *et al.*, 1979; Alberch, 1980; Gould, 1992). Heterochrony means phyletic "changes in the relative timing of appearance and rate of development for characters already present in ancestors" (Gould, 1977).

In accordance with De Beer´s concept of heterochrony (De Beer, 1940), the existence of the mouse vestigial tooth anlagen can be interpreted as "repetition" and their further integration into only one incisor anlage specified as "deviation", their extinction in the diastema as "reduction". Gould (1977) modified De Beer´s original classification of heterochrony and did not include "repetition" among heterochronic changes. From this point of view not the existence of the vestigial tooth anlagen by itself, but a phyletic change in timing and/or rate of development of relative structures causing alteration of the primary (original) ancestral teeth may be classified as heterochronic:

- The origin of the composite incisor anlage in the mouse could be explained by phyletic "predisplacement" (earlier start) and/or "acceleration" (Gould, 1977; Alberch *et al.*, 1979) of oral vaulting of the extradental mesenchyme at the periphery of the incisor domain, which might cause the integration of the individual primary dental laminae into the functional incisor dental lamina and so prevent their further independent development.
- Gaunt and Miles (1967) suggested that rodent toothless diastema originated as a result of differential growth rates of the dentition and jaw. In our opinion, this difference might result in tooth disappearance providing it occurred at early stages of dental development. We can hypothetically suppose a phyletic "predisplacement" and/or "acceleration" of the prenatal mesio-distal growth of the mesenchyme of the jaw segment situated between the mouse incisor and molar domains resulted in some alteration of epithelial-mesenchymal signalling with the underlying epithelial anlage of the dentition and, consequently, in a serious disturbance of tooth development.

Heterochronic changes are supposed to take place at various levels of biological organization and their manifestation at tissue level also has to include changes in timing of the appropriate tissue-interactions (Alberch *et al.*, 1979; Hall, 1984; Smith and Hall, 1990), as well as qualitative/quantitative changes of gene expression (Gould, 1992). According to Raff (1992): "The suppression of older genetic controls can be a key innovation, because it provides the basis for subsequent genetic modifications and additions". Heterochronic changes of gene expression during evolution could induce a chain of structural-functional changes manifested at cell, tissue and organ levels, the final result being modification or extinction of ancestral structures or initiation of a new structure in successors, as a prerequisite for functional adaptation. Even alteration of a single transcriptional product during ontogeny may result in establishment of a highly specialized anatomical structure (Maderson, 1975).

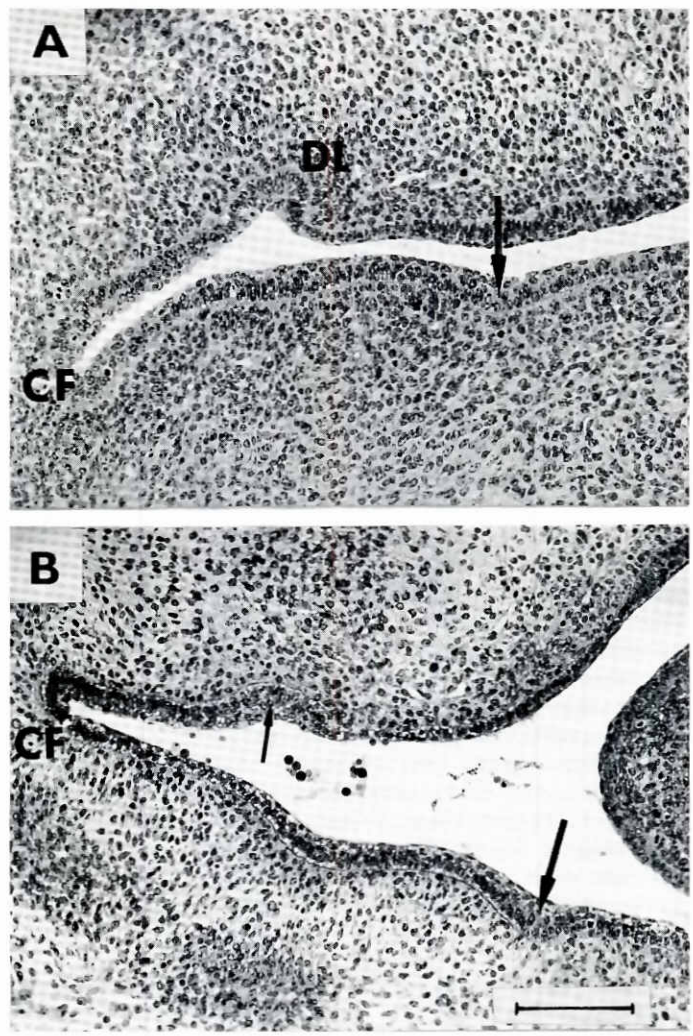

Fig. 9. Frontal histological sections documenting the existence of the low epithelial band (large arrow) in the mandibular diastema of the mouse embryos: (A) *Stage 12(24) and* **(B)**, *stage 13(24). Section was situated 110 μm and 125 μm from the foot of the mesial slope of the first molar anlage at stages 12(24) and 13(24), respectively. DL, the persisting distal end of the upper diastemal dental lamina; CF, cheek furrow. Note a similarity between the lower and upper (slim arrow) diastemal epithelial bands on day 13. Bar, 100 μm.*

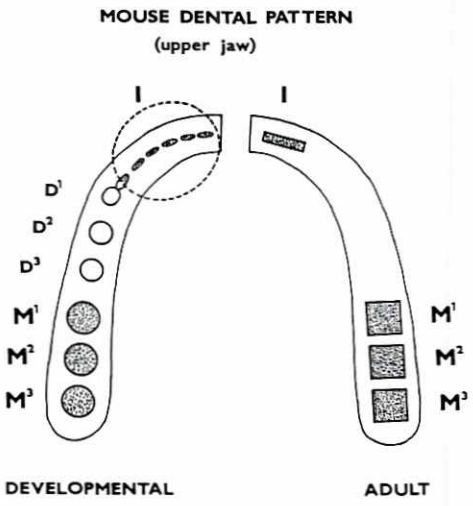

Fig. 10. Schematic representation of differences between the developmental and adult upper jaw dental patterns in the. *The developmental dental pattern includes the persisting (dotted areas) and transitory (empty areas) dental primordia. I, incisor; D1,D2,D3, the first, second and third diastemal dental rudiment, respectively; M1, M2,M3, the first, second and third molar, respectively. Dashed circle signifies reduction of the dental primordia (the primary dental laminae 1,2,3,M,4 and 5) in the incisor domain by their integration into one composite incisor anlage.*

Although the molecular basis of tooth initiation, patterning and early morphogenesis is not yet known, it has been suggested on a number of occasions that extracellular and cellular molecular factors play an important role in regulating tooth development (Kronmiller *et al.*, 1991, 1992; Thesleff *et al.*, 1991; MacKenzie *et al.*, 1991,1992; Mark *et al.*, 1992; Jowett *et al.*, 1993; Vainio *et al.*, 1993; Bloch-Zupan *et al.*, 1994; Satokata and Maas, 1994; Bégue-Kirn *et al.*, 1994; for recent reviews see Ruch, 1995; Sharpe, 1995; Thesleff, 1995). Establishment of the functional upper dental pattern in the mouse by phyletically determined reduction of the embryonic dental anlagen at specific positions during ontogenesis represents a model of hypodontia of evolutionary origin. From this point of view, the mouse embryonic upper jaw, where developmental processes associated with 3 specific segments of dentition can be compared (composite incisor, secondarily originating diastema, block of three molars), may represent a useful tool for molecular studies of control mechanisms on initiation, spatial organization and specific morphogenesis of teeth. Our descriptive data provide morphological prerequisites for such analyses at cellular and molecular levels, whose results, in turn, might elucidate the mechanisms underlying evolutionary trends (Raff, 1992).

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