Ontogenetic aspects of dental evolution

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CONTENTS

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Introduction

Comparative dental embryology arose in the last quarter of the nineteenth century, as a result of improvements of histological techniques (serial sectioning, reconstruction). In the hands of Röse, Leche, Kükenthal and others, and, later, Bolk, it was applied to problems of evolution, particularly to the relation between mammals and "lower" vertebrates. Study of the histological structure of the hard tissues (dentine, enamel, cementum) developed earlier, from about 1830, with improvements of the microscope and section-grinding technique: Owen's *Odontography* (1840-45) illustrates the microscopic structure of a wide range of recent and fossil teeth. Paleontologists, from G. Cuvier onwards, made use of dental characters in taxonomy, and from the 1870s onwards the evolution of mammalian molar cusp patterns was a topic of major interest (reviewed by Gregory, 1934). The present century has seen the rise of developmental biology, which seeks to unravel the causal connections of individual development by intensive experimental study of a limited number of laboratory species (as regards teeth, mainly the mouse and some amphibians). Evolutionary and developmental biology are complementary, and they increasingly interact (e.g. Smith and Hall, 1990, 1993). However, many evolutionary changes revealed by traditional comparative embryology have yet to be adequately explained in causal-developmental terms (Hanken, 1993).

In this paper I will briefly review some of the modifications of ontogeny that appear to have occurred during the evolution of the vertebrate dentitions from agnathans to mammals. Fossils provide only limited developmental information, and it is necessary to interpret them by comparison with seemingly similar living forms (Schaeffer, 1977). To a large extent the evolution of mammalian dental ontogeny has to be reconstructed from data derived from extant vertebrates that branched off long ago from the line leading to mammals (Fig. 1).

The evolutionary changes discussed relate to two phases of dental ontogeny: initiation and morphogenesis (Kollar and Lumsden, 1979). A tooth originates from an interaction between mesenchyme, derived from the neural crest, and epithelium. The locations at which the initiation takes place are influenced by local or regional differences among the reacting cells, and they change in the course of evolution, resulting in changes of the tooth-bearing regions, in the distribution of teeth within these regions, and in the mode of development of replacements. Epithelial-mesenchymal interaction sets going a process of morphogenesis, in which the tooth acquires a specific form. This involves growth and cytodifferentiation, culminating in the apposition of dentine and enamel. A great variety of tooth forms have evolved in vertebrates, especially in mammals, where regional differences have arisen within the dentition.

Dermal and oral teeth

The similarity to teeth of the dermal denticles (placoid scales) of elasmobranchs (Hertwig, 1874; Reif 1978a,b), and the presence of

dentinous "odontodes" in the exoskeleton of a wide range of Paleozoic agnathans and fishes (Orvig, 1967, 1968, 1977; Reif, 1982; Smith and Hall, 1990; Smith, 1991) seem to imply that teeth originated as products of the skin in jawless vertebrates, and that they subsequently spread to the mouth with the conversion of the mandibular arch into jaws in gnathostomes. Northcutt and Gans (1983) suggested that odontoblasts originally had an electrosensory function. The epidermal keratinous teeth of surviving agnathans (hagfish, lampreys) have been regarded as not homologous with true teeth (Lison, 1954; Youson, 1981).

This view has been challenged by the discovery of an enamelin in the teeth of a hagfish (Slavkin et al., 1983), and the recognition that the conodonts are vertebrate relatives (Aldridge et al., 1993). Conodonts possessed an oropharyngeal feeding apparatus, made up of a number of teeth of complex morphology, but no exoskeleton. Several types of hard tissue are found in their teeth, differing between the genera that have been investigated (Sansom et al., 1992, 1994): on the crown is a lamellar layer with apatite crystallites, resembling enamel; the basal tissues resemble forms of dentine, or bone and calcified cartilage, according to genus. Whether these structures are ancestral to teeth, or a parallel development, is unknown. Nasopharyngeal denticles have recently been found in an agnathan (Van der Bruggen and Janvier, 1993), showing that dermal denticles in the pharynx originated prior to the evolution of jaws.

Various hard tissues are found in Paleozoic vertebrates, and though they are broadly classified as enamel, dentine and bone they differ histologically in many cases from these tissues in mammals. Their phyletic relationships are debated (Orvig, 1967; Schaeffer, 1977; Halstead, 1987; Maisey, 1988; Smith and Hall, 1990, 1993; Lund et al., 1992). For example, some forms of dentine (mesodentine, semidentine) contain cell spaces and show an approach to bone, suggesting that odontoblasts and osteoblasts had a common origin. Dentine develops near the outer surface of the scale or tooth, as if formed under the influence of the overlying epithelium; in many cases it is covered on the crown by a layer of enamel-like tissue, and on the base by bone or an acellular tissue that Smith and Hall (1990) compared with cementum.

Dermal dentine has disappeared in most modern bony fish, but a layer is retained under the ganoin of the scales of the primitive actinopterygian *Polypterus* (Meinke, 1982), and denticles, resembling placoid scales, are present on the outer surface of the scales of *Latimeria* (Smith, 1972), *Polypterus* and *Lepisosteus* (Meinke, 1982; Meunier et al., 1988), and some siluroid teleosts (Bhatti, 1938). The cosmine layer of Devonian crossopterygians and dipnoans appears to have been formed phylogenetically by the coalescence of originally separate dentine tubercles; it is covered by a layer of enamel (Goodrich, 1908; Orvig, 1969; Thomson, 1975; Meinke and Thomson, 1983). In land vertebrates dentine is confined to the mouth, but dermal bones of the skull are of neural crest origin (Le Douarin et al., 1993), and bony dermal scales of fossil amphibia and extant Gymnophiona are probably derived from the exoskeleton of fish ancestors.
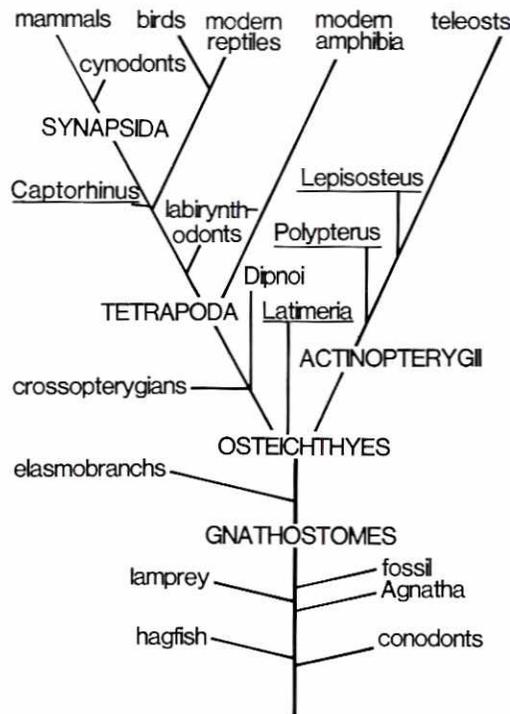
Fig. 1. A simplified phylogenetic tree of the vertebrates, to show the relationships of the forms mentioned in the text.

Although it has not yet been proved experimentally, it seems reasonable to assume that the dermal teeth of fishes, and the exoskeleton generally, are produced from neural crest mesenchyme, derived from the postcranial as well as from the cranial regions of the crest (Schaeffer, 1977; Halstead, 1987; Smith and Hall, 1990; Smith, 1991). Oral teeth, on the other hand, are derived from the restricted region of the cranial crest that in all vertebrates gives rise to the cartilages of the orobranchial region. The loss of dermal teeth therefore implies a loss of odontogenic function of the postcranial crest. In teleosts (zebrafish, Eisen and Weston, 1993; Smith *et al.*, 1994) and amphibia (*Pleurodeles,* Chibon, 1966) the postcranial crest no longer gives rise to dentine, but it continues to form connective tissue of the dermis and the dorsal fin. In the zebrafish, Smith *et al.* (1994) showed by injection of a fluorescent probe that neural crest cells are incorporated in the causal fin, where they probably form the lepidotrichia. In mammals and birds the postcranial neural crest contribution to connective tissue is diminished (Lumsden, 1988). How far these differences are due to changes in the neural crest or in the ectoderm with which it reacts is unknown. There is evidence that mammalian postcranial crest has retained some odontogenic potency, which is elicited by mandibular ectoderm but not by ectoderm from the limb bud (Lumsden, 1987, 1988). On the other hand, mouse molar papilla induces enamel organ in the skin of the foot (Kollar and Baird, 1970). Avian (quail) flank epithelium forms tooth-like structures with rabbit incisor papillae (Fuenzalida *et al.*, 1990), but the ameloblasts do not differentiate. The absence of oral teeth in birds (Kollar and Fisher, 1980) and in the lower jaw of anurans (Wagner, 1955) appears to be due to failure of epithelial-mesenchymal interactions, and the same might apply to the absence of dermal teeth.

Relation of oral teeth to bones

The most primitive arrangement of oral teeth appears to be a general distribution of denticles over the mouth lining, comparable with their distribution in the skin; such are the mucous membrane denticles of elasmobranchs (Peyer, 1968; Nelson, 1970; Reif, 1982). In bony fish the teeth become attached to the dermal bones that surround the mouth cavity, including the palate and the medial surface of the lower jaw, and small tooth plates are attached to the hyoid and branchial arches (Jarvik, 1944; Nybelin, 1968). Teeth on the vomer, palatine, pterygoid and splenial are retained in various amphibians, e.g. *Ambystoma* (Adams, 1924; Kerr, 1960), and reptiles (Edmund, 1969). In mammal-like reptiles (Kemp, 1982) these were lost after the Late Permian, with the development of the secondary palate, leaving teeth only on the premaxilla, maxilla and dentary, as in mammals.

Teeth develop separately from the underlying bone, to which in fish, amphibians, and many reptiles they become united by "bone of attachment", derived from the mesenchyme of the dental papilla. In the socketed (thecodont) teeth of other reptiles, e.g. crocodilians, and of mammals, papilla mesenchyme extends around the enamel organ to form a follicle. This deposits cementum on the root surface and alveolar bone externally, the intervening layer developing into a fibrous periodontal membrane (Berkovitz and Sloan, 1979; Osborn, 1984).

When characters of size or arrangement permit homologizing of teeth or tooth groups in different vertebrates, it is seen that there is a correlation between teeth and the bones that carry them; teeth and bones seem to evolve together (Fig. 2). Examples are: the enlarged labyrinthodont teeth on the vomer, palatine and ectopterygoid of crossopterygians and early amphibians; the row of teeth on a transverse ridge of the pterygoid in early synapsids; the canines near the anterior end of the maxilla in synapsids and mammals. Such relationships seem to imply a morphogenetic link between teeth and bones, but the nature of the link is not clear. At least in mammals, an important contribution to the jaw bones is made by alveolar bone, produced by the dental papillae (Atchley and Hall, 1991). It has probably evolved from the bone of attachment of more primitive vertebrates. The basal dermal bones appear as separate accumulations of neural crest mesenchyme; like the teeth, they are induced by epithelium (Tyler and Hall, 1977; Tyler, 1978; Hall, 1987), though, lying more deeply, a diffusible morphogen may be involved (Hall, 1981). The induction however is not specific, for ectopic epithelium can be substituted, and there does not appear to be a prepattern in the epithelium which might determine the location of dermal bones (Noden, 1983), such as Lumsden (1987, 1988) posited for mammalian teeth.

Spatial repetition

Teeth normally form separate units, arranged more or less equidistantly in rows or in fields over a surface, as on the palate of urodeles (Lawson *et al.*, 1971; Clemen and Greven, 1977, 1979), where they tend to form an alternating ("quincunx") pattern. In this respect they resemble other skin structures such as feathers and vibrissae. The regular arrangement of placoid scales of elasmobranchs is associated with a crisscross pattern of collagen fibres in the dermis; scales that regenerate after wounding are more irregularly arranged (Reif, 1978b). The linear arrangement of teeth at the jaw margins may be regarded as the result of the narrowness of the

tooth-forming area, for in many non-mammalian vertebrates they develop or are replaced as two alternating series (e.g. elasmobranchs, Reif, 1984; teleosts, Berkovitz, 1977; reptiles, Edmund, 1969; Osborn, 1973). In the Permian reptile *Captorhinus* the maxillary and dentary fields are wider and they bear several rows of teeth in an alternating pattern (Edmund, 1960; Bolt and De Mar, 1975; Osborn, 1977). The exostichos-endostichos concept of Bolk (1922) (see Peyer, 1968) and the Zahnreihe Theory of Edmund (1960) were based upon the alternating replacement of teeth. For critique of Zahnreihen see Osborn (1970, 1973) and De Mar (1972).

Teeth provide an example of the widespread phenomenon of merism (Bateson, 1894) or periodicity of pattern (Cooke, 1981), a subject that has not advanced far beyond the speculative level. Osborn (1971, 1974a) postulated an inhibitory zone around the developing tooth germ, due either to the diffusion of a specific substance, or to the tooth germ acting as a "sink" into which substances are drained from the surrounding tissue fluid. Reif (1978a, 1982, 1984) postulated inhibition to explain spacing of the odontodes of fishes. Westergaard and Ferguson (1987) suggested that the initiation of a tooth sets up a progress zone, perhaps by cell-cell contact, and a new tooth is initiated where a particular positional value is attained.

Any explanation must account for cases where teeth develop in close proximity or even unite. The tooth-plates of dipnoans are formed in phylogeny (Smith, 1977) and ontogeny (Kemp, 1979) by the union of originally separate teeth. Complex scales of fossil fishes were apparently formed by the accretion of odontodes (Orvig, 1968; Reif, 1978a). Reif (1982) supposed that in such cases the inhibitory fields were short-lived. Connation of mammalian teeth (e.g. Berkovitz and Thomson, 1973) is another example.

Osborn (1971), working on the lizard *Lacerta*, attributed the alternation to growth of the jaw, which by separating the first-formed teeth removed the intervening mesenchyme from inhibition. Subsequent studies of tooth initiation in reptiles (Westergaard and Ferguson, 1986, 1987; Westergaard, 1988) showed that the regular pattern did not apply to the earliest tooth germs; thus in the alligator the earliest teeth are in positions 3, 6, 12 and the intervening teeth appear as space is created by jaw growth. In mammals alternation has been lost, and initiation is related to the regional differentiation of the dentition: primitively in placentals the first teeth are an incisor (di1 or di2), canine (dc), and a multicuspid cheek tooth (usually dp3 or dp4) (Butler, 1963, 1978a; Osborn, 1978a).

Succession

Tooth production is repeated in time as well as space. Most vertebrates are polyphyodont, replacing teeth continuously throughout life. The number of teeth that develop successively at a given location can be very large: estimated at 200 in a shark (Reif, 1984), 45-50 in a crocodile (Poole, 1961). Restriction or absence of replacement is a derived state, as in mammals and some reptiles, such as *Sphenodon* (Robinson, 1976) and agamid lizards (Cooper et al., 1970).

Primitively the enamel organs of the successional teeth were formed, like those of the primary teeth, directly from the epidermal or oral epithelium, without the intervention of a dental lamina. This is the case in placoid scales (Reif, 1978b), denticles in the oral mucosa of elasmobranchs (Peyer, 1968), and the odontodes of the scales of agnathans and fossil fishes (Orvig, 1968; Meinke, 1982).

The lamina develops in elasmobranchs, amphibians and reptiles as an invasion of epithelium along the jaw, lingual to the rudimentary primary teeth that develop directly from the superficial oral epithelium; successional teeth form at the deep edge of the lamina and move up its labial surface as they develop (Woerdeman, 1921; Osborn, 1971; Reif, 1982, 1984; Westergaard and Ferguson, 1988). Palatine teeth of reptiles develop from another lamina, on their labial side (Woerdeman, 1919). Actinopterygian fishes show what may be a less advanced condition, in which there is a separate epithelial downgrowth from each primary enamel organ (Kerr, 1960; Berkovitz, 1977; Berkovitz and Shellis, 1978).

The series of teeth that develops from the same location on the lamina constitutes a tooth family (Bolk, 1922; Osborn, 1973). Irregularities sometimes occur: for example, in sharks a tooth may be replaced by two successors, or by a member of another family (Reif, 1984). Westergaard and Ferguson (1987) found similar irregularities in the alligator, and they doubted the reality of the family as a morphological unit. Osborn (1978a,b) on the contrary regarded a family as the product of a single clone of mesenchyme cells.

In mammals there are no rudimentary teeth prior to the development of the lamina, and the first functional teeth erupt late, probably because of lactation. Replacement is also retarded, so that distinct juvenile and adult dentitions can be recognized. The Triassic cynodont *Thrinaxodon*, of which a good growth series is known (Parrington, 1936; Osborn and Crompton, 1973), probably represents a stage through which the mammals have passed. The youngest specimen has 8 postcanine teeth, and four more were added posteriorly during growth. Replacement was alternating; at most five successive teeth were produced in the anterior positions and fewer, probably only two, posteriorly. Teeth ceased to be produced in the anterior positions in older animals, so that the functional region moved backwards with age. In *Diademodon* (Hopson, 1971; Osborn, 1974b) replacement is no longer alternating but sequential. Again, the functional region shifts along the series as teeth fail to develop in anterior positions and new teeth are formed posteriorly.

The lamina of cynodonts, represented by a groove in the dentary, persisted throughout life. In mammals it sooner or later disappears interdentally, leaving fragments ("replacement laminae") attached to the enamel organs of the primary teeth. In mammals the premolar region, where teeth are replaced, is distinguished from the monophyodont molar region (Owen, 1845). However, replacement laminae develop also in connection with the molars, and the difference between the two regions may not be absolute. In the Cretaceous mammal *Gobiconodon* (Jenkins and Schaff, 1988) the "molars" are replaced. McKenna (1975) believed that even in placentals the premolar-molar division was not fixed: failure to develop the last premolar would convert the milk-tooth into a permanent molar. Archer (1978) held that the milk-tooth of marsupials, usually called dp3, is not the predecessor of P3 but the first molar. For discussion of this and other embryological aspects of mammalian dental formulae, see Luckett (1993).

Development of individual teeth

A simple tooth develops from the tip downwards. Differentiation of odontoblasts and ameloblasts begins at the cusp tip, and proceeds basally as cells are recruited from a mitotically active basal zone. This type of accretionary growth produces a conical

shape with spiral curvature, as in the case of mollusc shells or the horns of ruminants (Thompson, 1942). The cusps of mammalian molars grow in the same way as simple teeth (Butler, 1956; Ruch, 1990). Passing up a tooth or cusp from base to tip, a sequence of stages can be traced, involving the interaction of the odontoblasts, ameloblasts and the intervening basal lamina, and leading to the deposition of dentine and enamel.

Development of these hard tissues has been most studied in mammals, and variations occur in other vertebrates, especially in fishes (reviewed by Lund *et al.*, 1992). Enameloid, found in fishes, and also in urodele larvae (Smith and Myles, 1971), is formed, internally to the basal lamina, from a collagenous matrix, produced by odontoblasts, into which ameloblasts secrete enamel proteins (Shellis and Miles, 1974; Shellis, 1978; Herold *et al.*, 1980). It calcifies before the dentine. The difference between enameloid and enamel seems to be one of timing of ameloblast activity, relatively to dentine development (Smith, 1992). In actinopterygian teeth, enameloid is formed near the tip, and enamel ("collar enamel") nearer the base. Likewise in many fishes more than one type of dentine is produced successively in the same tooth.

The basal lamina of the inner dental epithelium predetermines the form of the tooth. Although in land vertebrates the basal lamina disappears with enamel formation, its shape survives in the completed tooth as the dentine-enamel junction. In mammals it becomes complexly folded to produced a specific pattern of cusps, ridges and valleys, the details of which are under genetic control (e.g. in the mouse, Grüneberg, 1965). Folding is accompanied by cell division and differentiation in the ameloblast and odontoblast layers (Ruch, 1990); how far it is due to localized growth or to changes of cell shape (Ettensohn, 1985) is unknown.

Butler (1956) suggested that the folding was protected from distortion by the stellate reticulum, which exerts pressure by imbibition of water. At an earlier stage, an "enamel knot", a group of postmitotic cells derived from the inner dental epithelium, forms at the site of initiation of the first cusp. It produces a mitogen FGF-4 which probably stimulates the growth of the cusp (Jernvall *et al.*, 1994). Secondary enamel knots form transiently at the sites of other cusps. An enamel knot and stellate reticulum have been recorded in crocodilians (Westergaard and Ferguson, 1987). In most other vertebrates the enamel organ in a two-layered structure with little or no tissue between the outer and inner epithelia (Studnicka, 1900).

Development of tooth form in non-mammalian vertebrates has received little attention. Kerr (1955) noted in elasmobranchs that at the cutting edges of the teeth the basal lamina is thickened, and the ameloblasts are irregular and do not hypertrophy. In teleosts and urodeles Kerr (1960) found a process of reshaping, in which the cusp tip was converted from a dome shape to a point. In urodeles ameloblasts form a rosette, with their narrow ends pointing to the cusp tip (Smith and Miles, 1971). Woerdeman (1921) described in crocodilians longitudinal folds of the ameloblast layer related to ridges on the tooth. Reshaping occurs in human teeth while odontoblasts and ameloblasts are differentiating: the cusps become more acute and the crests more distinct (Turner, 1963).

Molar cuspidation in mammals

The evolution of multicuspid mammalian molars from unicuspid teeth has been debated since the 19th century (see Osborn, 1907; Gregory, 1934; Butler, 1941a, 1978b; Patterson, 1956; Bown and Kraus, 1979). It is now agreed that the original cusp is (in Osborn's
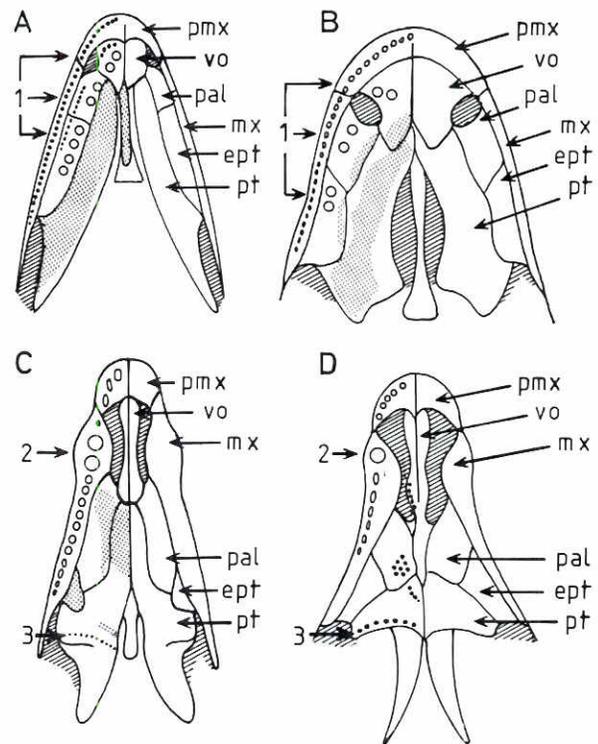
Fig. 2. Palates of (A) *Eusthenopteron* **(crossopterygian), (B)** *Edops* **(labyrinthodont), (C)** *Dimetrodon* **(early Permian synapsid), (D)** *Sauroctonus* **(late Permian synapsid).** *Tooth positions indicated on the left side of each drawing; stippled areas are covered with small teeth. Note (1) enlarged teeth on vomer, palatine and ectopterygoid in* **A** *and* **B***; (2) enlarged teeth (canines) in maxilla in* **C** *and* **D***; (3) transverse row of teeth on pterygoid in* **C** *and* **D***.*

nomenclature) the paracone on upper teeth and the protoconid on lower teeth; these are the mesio-buccal cusps in both jaws of man. New cusps have arisen from cingulum ledges at the margin of the crown or from crests on the slopes of older cusps. Paracone and protoconid are also the first cusps to form in ontogeny, the remaining cusps arising at various times and positions within the surrounding growth zone (Butler, 1982). The order of cusp initiation can vary between different mammals and between teeth in the same jaw (Butler, 1956). Developmental rates can also vary, so that the order of calcification and final height is not necessarily the same as the order of initiation. Cusp development in the mouse is described by Gaunt (1955, 1961); that of man by Turner (1963), Kraus and Jordan (1965) and Butler (1967, 1971).

The cusp pattern is affected by the shape of the crown as a whole, which seems to be due to unequal growth in the papilla, and is related to the root pattern. Upper molars of primitive marsupials and placentals are triangular in outline, with three roots; lower molars are oval or oblong with two roots. Roots are formed at the positions of greatest horizontal extension of the papilla. Their position is related to the distribution of blood vessels entering the papilla; Hertwig's sheath, growing below the papilla avoids areas where the vessels are most densely distributed, leaving foramina around which roots subsequently develop (Butler, 1956; Gaunt, 1960).

The relative independence of cusps in evolution and variation (Butler, 1952a,b, 1988; Axelsson and Kirveskari, 1982) lends
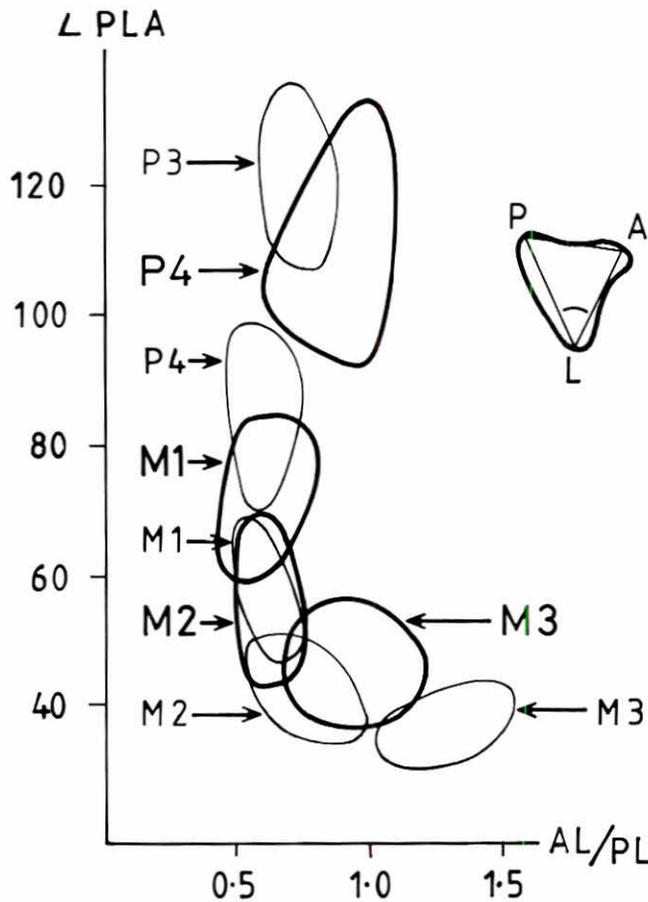
Fig. 3. An example of homoeosis in the dentition. Shapes of triangular teeth depicted by plotting the lingual angle against the ratio of the including sides. *The loops show the range of variation in two related species of insectivore: Hemicentetes semispinosus (heavy lines) and H. nigriceps (light lines). From Butler (1941b).*

support to the concept of the tooth surface as a mosaic of cuspal areas, each under specific genetic control. Ruch (1990) postulated that each cusp was formed from a clone of neural crest cells, perhaps from a single committed cell. This does not explain how the cusps come to be arranged in a pattern. The early tooth germ is capable of regulation. Glasstone (1963) grew complete teeth from partial rabbit molar germs, divided transversely prior to cusp formation, and Fisher (1957) obtained the same result with the mouse. Fisher also found that tooth germs explanted at 13-14 days frequently reversed symmetry, but Lumsden (1979) did not confirm this. Longitudinally divided tooth germs did not regulate. Cellular interactions within the early tooth germ need to be further investigated.

Heterodonty

The teeth of a vertebrate dentition generally differ in size, and also often in shape. Greater differences, especially between prehensile or incisiform anterior teeth and crushing posterior teeth, occur in some fish, e.g. the shark *Heterodontus* (Reif, 1984), and

reptiles, e.g. agamid lizards (Cooper *et al.*, 1970). The mammalian type of heterodonty first appeared in Lower Permian synapsids such as *Dimetrodon* by enlargement of teeth in the maxilla, forerunners of the mammalian canine. Premaxillary (incisor), canine, and postcanine regions became further differentiated in later synapsids (for details see Kemp, 1982). In elasmobranchs, Reif (1984) distinguished between two types of heterodonty: monognathic, due to serial differences between tooth families, and ontogenetic, due to differences within families. The break in pattern between mammalian molars and premolars is ontogenetic, as it reflects the difference between the premolars and the milk-molars that they replace. Three types of teeth developed successively at each postcanine locus in *Thrinaxodon* (Osborn and Crompton, 1973), and in *Diademodon* there may be as many as six (Osborn, 1974b); heterodonty of the post-canine dentition of these cynodonts is mainly ontogenetic, due to teeth of different generations being in place at the same time.

Differences between adjacent teeth are quantitative, and even minor details can be homologized (Butler, 1937). In their variation and evolution teeth display homoeosis (Bateson, 1894), whereby patterns are transferred from one tooth to another. In perissodactyls, the molar pattern extended forwards through the milk-molars, and premolars came to resemble the corresponding milk-molars (Butler, 1952a,b). The postcanine region evolves as a unit, though the number of component teeth may change; the pattern of a tooth depends on its position in the series, so that, for example, last molars have a characteristic shape, irrespective of their numerical position. *Otocyon* has three upper molars whereas other dogs have two; M3 of *Otocyon* resembles M2 of other dogs, and M2 is similar to M1 (van Valen, 1964). Homoeotic shifts of tooth pattern are frequently accompanied by changes in the position of the teeth in relation to the skull and jaw muscles (Butler, 1941b, 1978a) (Fig. 3).

Butler (1939) hypothesized that the forms of the teeth were determined by a morphogenetic field, the position of which, relatively to the tooth locations, could change in the course of evolution. Incisiform, caniniform and molariform teeth were determined by three districts within the field. Osborn (1978a) ascribed the differences between teeth to changes in the neural crest mesenchyme as it spreads along the jaws; the three tooth groups are the product of different clones of mesenchyme cells. After producing a "stem precursor" the clone grows forwards or backwards, gradually losing its "shape potential" with repeated mitoses. Lumsden (1979) found that the prospective molar region of the mouse could, when explanted, give rise to the three molars in order; the patterns are simplified from M1 to M3, in accordance with the loss of potential postulated by Osborn.

Kollar and Baird (1969) and Héritier and Dominatti (1970) reciprocally recombined enamel organs and papillae of mouse incisors and molars, and found that the resulting teeth agreed in type with the papilla. However, in younger embryos (<11.5 days) induction is by the epithelium (Dryburgh, 1967; Miller, 1969; Mina and Kollar, 1987; Kollar and Mina, 1991). Regional differences exist in the jaws before the appearance of teeth (Langille, 1993). The transcript of the gene Hox-7, which is involved in epitheliomesenchymal inductions (Takahashi *et al.*, 1991), appears in the jaw with the invasion of neural crest mesenchyme; it becomes concentrated at the anterior end, in mesenchyme and adjacent epithelium, and later in the dental papillae (Robert *et al.*, 1989). Segments of mouse jaw grown *in vitro* (Glasstone, 1967) or in the anterior chamber of the eye (Lumsden, 1987, 1988) developed

incisors only near the anterior end, molars more posteriorly. Lumsden found that incisors were formed only in a small area near the mandibular symphysis, and in the frontonasal process. He concluded that neural crest mesenchyme is unspecified when it enters the jaw during the 9th and 10th days, and teeth are formed only when it contacts tooth-specific epithelium. He suggested that a prepattern in the epithelium determines the distribution and the type of teeth.

Bateson (1894) compared teeth, in their mode of variation, to other meristic structures, such as arthropod segments, and vertebrate somites, vertebrae and digits. It seems reasonable to suppose that the dentition will have analogies to these structures in its morphogenesis. In those cases which have been most investigated, three types of interacting processes can be distinguished: (1) positional information (Wolpert, 1969, 1981; Wolpert and Stein, 1984) is specified by a morphogen, spreading by diffusion or cell-cell contact, and giving polarity to the system. (2) The material is organized into a series of units (segments, somites, digits) (Cooke, 1981). (3) The units differentiate under the control of homeobox genes, whose fields of expression form a nested set (Gehring, 1987; Graham *et al.*, 1989; Kessel and Gruss, 1990). In *Drosophila* (Ingham, 1988) the initial gradient is due to maternal genes such as *bicoid,* which control the transcription of the gap and pair-rule genes, and segment diversity is controlled by homoeotic genes of the antennapedia-bithorax complex. Head-tail polarity of the vertebrate mesoderm is established at gastrulation (Ruiz i Altaba and Melton, 1989; Smith, 1993), somites are formed sequentially over a period of time (Cooke, 1975), and their differentiation is controlled by combinations of homeobox genes (Kessel and Gruss, 1991). Anterior-posterior polarity of the hand is determined by diffusion, probably of a retinoid, from a zone of polarizing activity, resulting in the sequential expression of a series of homeobox genes (Tabin, 1991).

Does the mammalian dentition develop in an analogous way? It is tempting to think of the epithelial prepattern as a consequence of, or aspect of, a system of positional information in the face (Langille, 1993). It is conceivable that it is regional only, and that the numbers of tooth locations within each region are determined by a separate mechanism. Genes, at present unidentified, would be expressed in tooth germs at appropriate levels of the positional gradient, resulting in the range of patterns. There is also the problem of timing: is the pattern of the whole dentition determined over a short period, its effect remaining latent in the late-developing molars and replacing premolars? Lumsden (1978) suggested the existence of a progress zone at the posterior end of the lamina; to account for ontogenetic heterodonty, other progress zones could be imagined in the replacement laminae of the antemolars.

Conclusion

As the articles in this special issue demonstrate, experimental research on tooth development is based very largely on murid rodents. The dentition of the mouse, with its highly specialized incisors, small number of teeth, absence of tooth-replacement, and distinctive molar patterns, is by no means typical of mammals in general. Likewise, the mammalian dentition diverges in many ways from those of other vertebrates. Extrapolation from the mouse to vertebrates in general must therefore be made with caution; it is highly desirable that the results obtained from mammals should be tested on other animals. Amphibians, the classic subjects of experimental embryology, have contributed much information, but

so far their tooth development has been little studied at the cellular and molecular levels. The introduction of the zebrafish, a teleost, as an experimental species (Eisen and Weston, 1993) holds promise of a better understanding of dental development in fishes.

Some ontogenetic processes were established very early in vertebrate evolution and are highly conserved. The neural crest is present in the lamprey, and dentine and perhaps enamel occurred in Ordovician vertebrates, so epithelial-mesenchymal reactions were presumably established at that time. Other features, such as oral teeth, their attachment to bones, and their replacement by means of a dental lamina, arose later. Several mammalian characters evolved in synapsid reptiles, especially Triassic cynodonts: alveolar implantation, with the distinction between crown and root; heterodonty, with differentiation of the canine and multicuspid postcanine teeth; limitation of tooth replacement; loss of palatal teeth. Possibly stellate reticulum and stratum intermedium developed in the enamel organ at that stage. Some of these characters evolved independently in other reptiles: crocodiles have stellate reticulum and alveolar membrane and agamid lizards have heterodonty and limited replacement. Mammals appeared in the late Triassic (about 200 million years ago), and since then they have greatly diversified in tooth pattern, dental formulae, and enamel and dentine structure.

Interpretation of these changes by developmental biologists is still at an early stage. Problems of patterning are particularly poorly understood. Why does the dentition develop as separate teeth? Is some form of inhibition involved? Are the sites of tooth initiation predetermined in the epithelium or is clumping inherent in the mesenchyme? Again, what cell interactions take place within the early papilla, and how do they predetermine the pattern of the tooth? On a larger scale, there is the problem of heterodonty: why do teeth in the same jaw develop differently? Attempts to answer such questions bring us up against some aspects of development that are of much more general application than to the teeth alone.

Summary

The evolution of dental ontogeny in the vertebrates is reviewed. Teeth probably originated as dermal structures, which secondarily spread to the mouth, where they became associated with bones. Tooth formation is a repetitive process, resulting in spatially separate units, and primitively it continued throughout life. Development of conical teeth commences at the tip and extends basally; folding of the basal lamina of the inner dental epithelium results in complex shapes, as in mammalian molars. Heterodonty, the divergent development of the teeth in a dentition, has evolved in a number of vertebrates, particularly mammals. Experimental analysis of dental development is still at an early stage, and the explanation of evolutionary changes in developmental terms is largely speculative. Mammals are atypical vertebrates in many ways, and more studies of lower vertebrates, especially fishes, are needed.

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