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Evolution of development of the vertebrate dermal and oral skeletons: unraveling concepts, regulatory theories, and homologies

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Abstract.—It has been contended that Reif's odontode regulation theory is a rival and alternative to Stensiö and Ørvig's lepidomorial theory as means of explaining the evolution of development of the vertebrate dermal and oral skeleton. The lepidomorial theory is a pattern-based theory that provides a homological framework that goes further than the odontode regulation theory in comparing dental papillae and their products, and it provides an explanatory mechanism for such relationships a posteriori. In contrast, the odontode regulation theory is process-based and observes only developmental similarity, providing no means of identifying homologies beyond this. The lepidomorial theory is superior to the odontode regulation theory in its ability to trace homology through the evolution of development of the dermal and oral skeleton. The criteria proposed to identify homology between scales—either within a given individual or taxon, or between different individuals or taxa—are, primarily, vascular architecture and, secondarily, external morphology. External morphology may be excluded on Reif's argument for the overarching principle of differentiation, a hypothesis supported by recent advances in the understanding of dental morphogenesis. Vascular architecture is potentially useful but appears to be determined by tooth/scale morphology rather than reflecting historical (phylogenetic) constraint. Data on the development of epithelial appendages, including teeth, scales, and feathers, indicate that individual primordia develop through progressive differentiation of originally larger, homogenous morphogenetic fields. Thus, there is no mechanism of ontogenetic developmental concrescence, just differentiation. Phylogenetic patterns of concrescence and differentiation are similarly achieved through ontogenetic developmental differentiation, or a lack thereof. In practice, however, it is not possible to distinguish between patterns of phylogenetic concrescence and differentiation because there is no means of identifying homology between individual elements within a squamation, or a dentition (in almost all instances). Thus, phylogenetic patterns of increase and decrease in the numbers of elements constituting dentitions or dermal elements are best described as such; further attempts to constrain precise underlying patterns remain without constraint and outside the realms of scientific enquiry. The application of the homology concept in the dermal and visceral skeletons is explored and it is determined that odontodes are serial homologs, conform only to the biological homology concept at this level of observation, and are devoid of phylogenetic meaning. It is concluded that Reif's theory is close to a universal theory of the evolution of development for the dermoskeleton and dentition, and additional components of theory, including the regulatory basis of temporal and spatial patterning, are tested and extended in light of data on the development of the chick feather array. Finally, the dermoskeleton is identified as an exemplary system for examining the regulatory basis of patterning and morphogenesis as it encompasses and surpasses the repertoire of established model organ systems.

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Introduction

Teeth and scales are among the most abundant and most readily fossilizable components of the vertebrate skeleton and it is not surprising, therefore, to discover that they have played a significant role in phylogenetic reconstruction and the classification of both fossil and living vertebrates (e.g., Agassiz 1833–1843; Owen 1845). Attempts to trace these skeletal structures have developed in hand with the primary concept in comparative anatomy, homology. Indeed, the most pressing problem in comparative biology, the reconciliation of anatomical, developmental, and historical concepts of homology (e.g., de Beer 1971; Wagner 1989), was attendant in the late nineteenth century when anatomical (paleontological) and embryological approaches to tracing homology in reptilian and mammalian dentitions first clashed. Similar attempts had been underway in the dermal skeleton, stemming from Williamson's (1849,

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1851) use of placoid scales from extant sharks as conceptual units in comparative analysis. Subsequently, various authors have formulated evolutionary hypotheses in which placoid scales have figured centrally as conceptual building blocks in the evolution and evolution of development of vertebrate teeth and scales (e.g., Hertwig 1974a,b; Ørvig 1967, 1968, 1977; Reif 1982a).

Most notable among these debates are the issues of concrescence (assimilation/coalescence) and differentiation (increased morphological specialization and/or division of elements) as patterns in the evolution of teeth and scales, and the developmental mechanisms that underlie these patterns. Although on face value this a subject is of little more than esoteric value, recent approaches to understanding the basic principles of organogenesis in vertebrates have broadened the significance of these issues and debates. The development of teeth, among the simplest of all vertebrate organs (Jernvall 1995; Stock et al. 1997), has been studied at ever increasing resolution such that the controls that directly underpin patterning and morphogenesis are beginning to be understood (e.g., Peters and Balling 1999). From what is known already, it is clear that many of the aspects of tooth development in laboratory animals, such as the mouse, are common to the teeth of other mammals (e.g., Keränen et al. 1998, 1999), and to the developmental programs of other epithelial-appendage organ systems (such as feathers, hair, and mammary, sebaceous, and sweat glands) of other vertebrates as well as invertebrate metazoans (e.g., Krejsa 1979; Thesleff et al. 1995; Chuong 1998). Given the degree of conservation in induction and patterning mechanisms, we may be confident in implicating their activity in the patterning and morphogenesis of organisms that have yet to be studied experimentally, and in those taxa known solely from paleontological data. Thus, we may begin to use these new data in attempting to reconcile long-standing disputes regarding the evolution of patterning and morphogenesis in these organ systems. In turn, the fossil record provides data on extinct clades of vertebrates that are obviously not open to experimental analysis. Most critically, the organisms in which this developmental system first evolved are entirely extinct and we have no recourse but to paleontological data in attempting to trace and understand the origin and early evolution of this developmental system.

Before reviewing established models for patterning the vertebrate dermal and visceral skeleton, it is worth noting precisely what this encompasses. The vertebrate skeleton is widely perceived as two distinct systems that have quite different developmental and phylogenetic backgrounds (Patterson 1977). The endoskeleton, which is composed of the vertebrae and associated axial structures, the limbs, the brain case, and various components of the skull, is the skeleton that is most familiarly vertebrate. However, the dermal and oral skeleton, which is composed of the teeth, scales, fin spines, and dermal bones of vertebrates, particularly lower vertebrates, is primitively the most extensive and, although not the most primitive, is the first to appear in a mineralized form, both geologically and phylogenetically (Donoghue and Aldridge 2001; Donoghue and Sansom 2002). This paper concerns only the evolution of development of the vertebrate dermal and oral skeleton.

In the recent literature on the evolution of development of the vertebrate skeleton, the terms ''dermoskeleton'' and ''exoskeleton'' have been used interchangeably. In this sense, the exoskeleton is used as an antonym to the ''endoskeleton,'' but there are two main reasons why this is not an altogether accurate or appropriate description of this skeletal system. First, the vast majority of the ''exoskeleton'' develops within the dermis and, thus, may more appropriately be assigned to the dermoskeleton (dermal skeleton) (Francillon-Vieillot et al. 1990). Strictly, the exoskeleton is restricted to keratinous elements such as horns, nails, claws, hairs, feathers, etc. Separating these into separate systems may be little more than semantic and may actually be entirely inaccurate from a historical, rather than a developmental, perspective. However, there remains potential for confusion through synonymy of the dermoskeleton and exoskeleton. This stems from suggestions that the difference in epithelial sources between true

''dermal'' skeletal elements, such as scales, and endothelial teeth (and oral scales) imparts real difference to two systems that are argued to have been distinct since early in vertebrate phylogeny (Smith and Coates 1998, 2000, 2001). Thus, although experimental evidence indicates that the patterning mechanisms underlying dental development are precisely similar to those controlling components of the dermoskeleton (see, e.g., Peterková et al. 2000), the distinction is maintained.

Finally, it is worth noting that a further dichotomy exists that cuts across any topological subdivision of the ''exoskeleton'' into oral and extra-oral systems. These are the odontogenic and skeletogenic scleroblastic ectomesenchymal cell lineages that are responsible for the dental elements (teeth and toothlike structures) and bony plates (respectively) in the dermal and oral skeleton. Although experimental evidence in support of this has come to light only relatively recently (Palmer and Lumsden 1987; Smith and Hall 1990, 1993; Atchley and Hall 1991; Vaahtokari et al. 1991), empirical evidence for separate developmental backgrounds has been known for some time (e.g., Westoll 1967). Quite surprisingly, established theories concern only the odontogenic component, addressing the skeletogenic component as though it were only a minor component of a holistic odontogenic scleroblastic system. As this contribution attempts to test these theories, the skeletogenic system will not be addressed.

Historical Review of Patterning Concepts and Theories

Early Work.—The earliest attempts to unravel the nature of development and patterning of the vertebrate dermoskeleton and visceral skeleton place central importance upon the nature of the placoid scales in living sharks. These began with Williamson (1849, 1851) who was among the first students of paleohistology and the first to provide a detailed account of the histology of Recent shark scales. On this basis, Williamson developed a theory in which the cosmine scales of basal sarcopterygians had developed through the amalgamation, or ''concrescence,'' of units equivalent to placoid scales. However, and although Williamson identified intermediates between placoid and cosmine conditions, he did not necessarily suggest that these represent an evolutionary sequence (which is not surprising given that Williamson's work was undertaken at least ten years before the publication of *The Origin*). Williamson's observation of ''analogy'' between placoid and cosmine structure were given an evolutionary slant by subsequent authors such as Hertwig (1874a,b; 1876, 1879, 1882) and Goodrich (1907), who appear to have assumed the primitiveness of the placoid condition. Hertwig and Goodrich turned Williamson's hypothesis of concrescence in the development of scales to one of concrescence in the evolution of development of scales and dermal bones. For instance, Hertwig's main argument was that teleost scales and large dermal bones developed through the concrescence of placoid scales such that the scale-bases fused into a single mass and, eventually, the surmounted denticles were lost. In contrast, Klaatsch (1890) appears to have proposed the first differentiation hypothesis, arguing that scales and plates develop from a single denticle in which the basal plate has become much enlarged.

Despite the generally widespread acceptance of concrescence mechanisms as explanations for the diversity of skeletal structures met with in the dermal skeleton, evolutionary studies of dental patterning have had little truck with concrescence as a transformational mechanism. Nevertheless, the shift from simple homodont coniform dentitions of mammalian antecedents to complex heterodont molariform dentitions of mammals has tempted many authors to suggest that the cusps of complex teeth arose through amalgamation of simpler teeth (e.g., Ameghino 1884, 1896, 1899; Adloff 1916; Bolk 1912, 1922; Kükenthal 1893; Röse 1892; Winge 1883). Concrescence continues to be raised as both a developmental and a phylogenetic mechanism (e.g., Peterková et al. 2000).

The Lepidomorial Theory.—During the middle part of the twentieth century, Erik Stensiö and Tor Ørvig developed a theoretical model that attempted to explain the patterning of the dermal skeleton, to resolve between skeletal elements both within and between taxa, and the

mechanism through which evolutionary transformations occurred. The ''lepidomorial theory'' was developed from a study of Paleozoic chondrichthyan scales that was never published (Stensiö and Ørvig 1951–1957); only the main conclusions of the theory ever made it into print. The first reference to this theory was made by Jarvik (1948), and it was outlined in greater depth by Ørvig (1951) and Stensiö (1958, 1961, 1962, 1964). The basic tenet of the theory (as published) is that the dermal and oral skeleton is, at its most basic level, the product of developmental modules termed *lepidomoria.* Each lepidomorium could be recognized on the basis that it was composed of ''an enamel-coated crown of dentine and a basal plate situated in the corium. To judge from the two canals leading out from its pulp cavity each lepidomorium arose ontogenetically from a simple corium papilla formed around a single vascular loop which ascended in a superficial direction from the sub-epidermal vascular plexus of the corium'' (Stensiö 1961: p. 236) (Fig. 1A–F). Subsequent development was perceived to follow the pattern typified by placoid scales; enameloid develops immediately adjacent to the enamel organ, constituting a rigid mold in which dentine begins to form; as such, the scale attains its definitive size and shape at once. Dentine forms apically first, and basally second, and the plate tissues begin to develop in coordination with the basal dentine.

As described, the lepidomorial theory is little more than a generalized description of the development of a placoid scale, as set out by Hertwig (1874a) and Klaatsch (1890). Although it is a concrescence-based model, it departs significantly from earlier theories in its interpretation of placoid scales. Modern shark scales had traditionally been held to reflect the primitive condition for the dermal skeleton, firstly because sharks were thought to be extremely primitive, but also because placoid scales are structurally simple. However, after studying the scales of a group of poorly known Late Paleozoic chondrichthyans (Fig. 1G–K), Stensiö and Ørvig (1951–1957) reached the conclusion that the basic structural unit of the dermal skeleton is a scale that is morphologically and structurally simpler than the condition met with in placoid scales. Most specifically, these authors argued that the simplest of all scales are vascularized by a single capillary loop that enters the pulp cavity from below and exits via a canal in the neck of the scale (Fig. 1G). Thus, because placoid scales possess supernumerary neck canals (Fig. 1A–F)—Stensiö (1961) cites a range of typically 3–15 or more per scale—they must be derived from the coalescence of as many ''primitive'' scales, or *lepidomoria.* In this view, placoid scales are neither simple nor primitive, but extremely complex and highly derived. Far from suggesting that scales actually coalesced to form a single larger scale, Stensiö and Ørvig (1951–1957) suggest that the primordia, the lepidomoria of these scales, coalesced (Fig. 1A) and, thus, there is no record of this transformational event in the mineralized tissues, other than the occurrence of supernumerary neck-canals (Fig. 1B–F).

Not only does the lepidomorial theory argue that morphologically complex scales and teeth arise through coalescence, but it also implicitly precludes differentiation as a mechanism for morphological change. Immediately after its inception, the lepidomorial theory became extremely influential and provided the criterion upon which entire orders of fish were classified (Stensiö 1958, 1964). Further, Stensiö (1961) argued that the lepidomorial theory provided the explanatory medium for evolutionary transformation between dental types, and most particularly for Cope (1883, 1889), Winge (1883) and Osborn's (1907) theories of increased complexity of tooth morphology, through the amalgamation of teeth of simple morphology.

The Odontode Concept.—Beginning with Ørvig (1967), a new concept, the ''odontode'' was conceived. At an operational level, there is little to distinguish between lepidomoria and odontodes; Ørvig's most precise definition of the concept was (Ørvig 1977: p. 54) ''special hard tissue units, or dental units, which generally speaking have those developmental and structural properties in common with the teeth of the jaws (whenever such are present) that they (a) each develop ontogenetically in a *single, undivided dental papilla* of mesenchymal soft tissue, bounded at its circumference by an *epithelial dental organ* in the adjoining dermis, (b) consist of *dentine* or, in

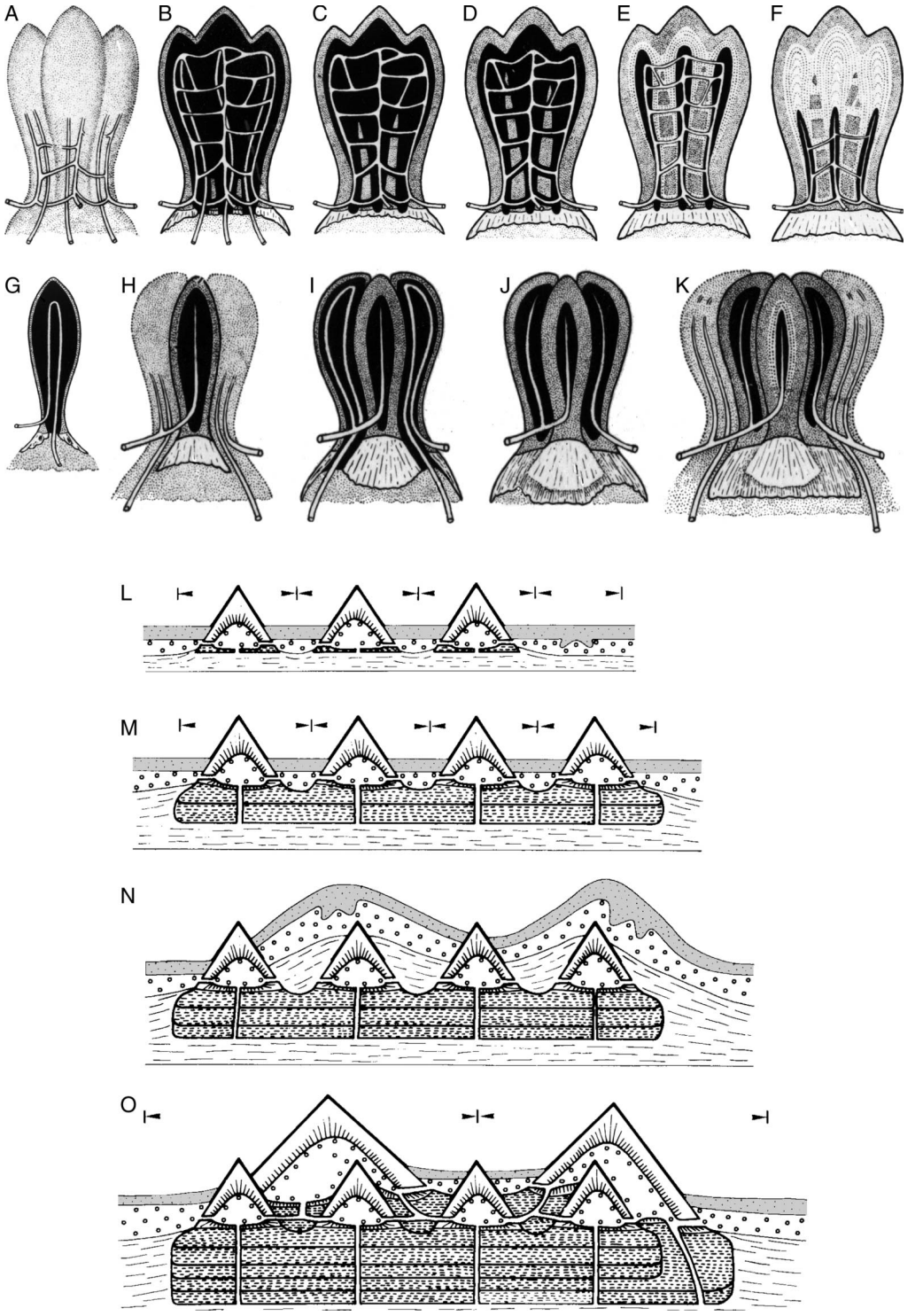

FIGURE 1. A–K, The lepidomorial theory, from Stensiö 1961 with the permission of Toronto University Press; L–O, The odontode regulation theory, from Reif 1982a. A–F, Diagrammatic representation of the hypothetical sequence of development of a placoid (synchronomorial) scale as envisaged by Stensio and Ørvig (1951–1957). G–K, Sequence of development of a cyclomorial scale based upon edestid scales from the Permian of Greenland. L–O represent the basic tenets of the odontode regulation theory, in which scales suppress development of new scale primordia by exerting a ''zone of inhibition'' upon the adjacent dermis. New scales develop through growth of the dermis, leading

some forms, *dentinous tissue* . . . and (c) frequently (but not always) possess a superficial layer of *enameloid.* At the same time, however, odontodes are in general terms also characterized by (d) not belonging to the dentition sensu stricto but to other parts of the dermal skeleton (sometimes including those immediately adjoining the dentition), (e) not, as a rule, fulfilling similar *functions* as teeth, (f) not forming in a submerged position in connection with a dental lamina or single, ingrowing epidermis digitations but always in *the superficial part of the corium* . . . because of which they are not replaced from below or sideways in a manner of teeth in the great majority of fishes, and (g) in many cases, not reaching nearly the same height (from top to base) as teeth.'' It is clear from Ørvig's later papers that he was attempting to draw a distinction between the odontode, as a concept, and lepidomoria, as theoretical developmental units; i.e., he was attempting to distinguish pattern from process. For instance, Ørvig (1977: p. 55) argues that the recognition of an odontode is a purely descriptive observation, that does ''not involve interpretation and can be applied irrespective of whether or not one adopts lines of reasoning such as those e.g., the lepidomorial theory (sensu Stensiö 1961). Odontodes, for instance, can just as well be single lepidomorial crowns as multi-lepidomorial formations of all degrees of complexity when they are analyzed on the basis of that theory.'' Although this was not stated explicitly at the point of inception of the odontode concept, it is clear from Ørvig's usage of the concept in his intervening papers that he intended this meaning implicitly. For instance, in dealing with the dermal skeleton of the placoderm *Romundina stellina*, Ørvig states that ''although all these tubercles certainly qualify as single odontodes (sensu Ørvig 1967, 1968), there is every reason to assume that each of them has arisen phyletically by the fusion of a group of considerably smaller odontodes of a kind existing in the dermal skeleton of ancestral forms. These latter odontodes are naturally no more identifiable as such, but are nevertheless frequently traceable by the nodules or cusps on the tubercles referred to above. Since there are here, as mentioned, occasionally also cusps associated with side-cusps, some of the original odontodes by the coalescence of which the tubercles formed were presumably bi- or tricuspidate elements'' (Ørvig 1975: p. 44). Nevertheless, Ørvig demonstrates reluctance to disassociate entirely pattern from process and this is clear even in the paper in which he attempts to draw a firm distinction between the recognition of morphogenetic units (the odontodes), and the interpretation of their transformational relationships, i.e., between a concept and a theory. In the case of cosmine, Ørvig (1977: p. 66) argues that the odontodes have ''fused so completely with each other in a horizontal direction . . . that they lost their original ability to form separately, each in a dental papilla of its own, and all arose within one single large dental papilla with the same extent as the cosmine sheet as a whole. . . . In this case it seems far more appropriate to speak of component hard tissues units . . . than of component odontodes. It is, in fact, each individual cosmine sheet which according to the definition above should deserve to be referred to as an odontode, but this usage is obviously awkward, and it is not adopted here.''

In summary, Ørvig's odontode is an operational concept for the recognition of morphogenetic units within mineralized dermal skeletons. Although at first the distinction between odontodes and their hypothetical transformational cousin, the lepidomoria, was poor, Ørvig eventually massaged his odontode concept to one of pattern recognition, free of the transformational hypotheses that burden the lepidomorial theory and its associated terminology.

The Odontode Regulation Theory.—Subsequently, Reif converted the odontode from a concept to a theory of morphogenesis to rival

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to gaps in the zones of inhibition, through shedding of established scales, or through cessation in the inhibitory effects of established scales such that new primordia develop on top of existing scales. Reproduced with amendment from Reif 1982a, with the permission of Plenum/Kluwer Publishing.

the lepidomorial theory in its explanatory power. Reif's work began by testing the premise upon which the lepidomorial theory was based: the existence of lepidomoria (Reif 1973). Reif attempted this by examining the development of placoid scales, Stensiö's type example of a scale derived from the concrescence of many lepidomoria. Reif (1973, 1974) found that at no stage in the development of placoid scales is there any evidence of differentiation of dental papillae into a series of distinct ''lepidomoria'' and, thus, the basic assumption and explanatory mechanism of the lepidomorial theory would appear to be have been falsified (and with it the theory upon which it forms the basis).

Reif's perception of the odontode is much the same as Ørvig's, except on two key points. First, Reif (1982a) incorporates teeth into his concept of the odontode, whereas Ørvig reserved odontodes to encompass all toothlike structures that are not actually teeth. Second, and more important, Reif rejects Ørvig's contention that the odontode concept is tenable irrespective of whether one accepts transformational theories. Instead, Reif (1982a) developed Ørvig's (1967, 1968, 1977) atomistic odontode concept into a transformational theory by augmenting it with the axiom that morphological changes take place through differentiation. It is not surprising then that Reif finds that ''I do not agree with Ørvig's (1977) statement that the odontode concept can be worked with irrespective of whether or not one accepts the Lepidomorial Theory. My view is that the Odontode-Regulation Theory is an alternative to the Lepidomorial Theory'' (Reif 1982a: p. 288). In other words, after Ørvig's attempt to separate the collection of morphogenetic data from the interpretation of transformational mechanisms, Reif (1982a,b) augmented the odontode concept with a new transformational hypothesis, and then objected to Ørvig's usage of the odontode concept.

Reif's odontode regulation theory (Reif 1982a,b), like the theories erected by Williamson, Hertwig, and Goodrich, assumes the primacy of the placoid scale as reflecting the basic morphogenetic unit within the vertebrate dermal skeleton. Nevertheless, Reif's theory differs from these in its contention that the principal mechanism of evolutionary change is differentiation of scale primordia. Thus, large or complex teeth and scales arise through changes in the morphogenesis of individual primordia, rather than through the concrescence of primordia. Reif (1982a,b) argued that the disparity of dermoskeletal types met with in both extant and extinct vertebrates can be explained through a combination of morphogenetic differentiation and temporal and spatial changes in development (in particular, see Reif 1980a) (Fig. 1L–O).

Comparing and Evaluating the Lepidomorial and Odontode-Regulation Theories

Despite its influential nature, the lepidomorial theory has attracted criticism from embryologists, and comparative anatomists studying extinct and extant taxa alike (e.g., Zangerl 1966, 1981; Peyer 1968; Gross 1973; Reif 1973, 1974, 1978a, 1982a; Maisey 1988). However, the greatest problems with the lepidomorial theory lie with the fact that the data and arguments upon which it is based were never published, leaving to the published record only short and confusing summaries of the implications and conclusions of the work (e.g., Ørvig 1951; Stensiö 1961, 1962; Jarvik 1960). And further, the theory ''evolved'' through time such that its explanatory power appears to have varied in scope. Thus, the theory has proven difficult to test and, as will be demonstrated, has not been tested. This would not be problematic if the theory could be rejected out of hand. But the theory continues to be influential to this day, both formally (e.g., Karatajute-Talimaa 1992, 1998), and informally, in terms of the concepts that it encapsulates (e.g., Peterková et al. 2000). Further, as will be demonstrated below, its putative rival, the odontode regulation theory, requires a rejection of the lepidomorial theory in its formulation. What is required, therefore, is an unambiguous explanation of how the lepidomorial theory was formulated, to provide both a means of erecting tests of the theory, and a means of understanding its relationship to the odontode regulation theory.

A manuscript (Stensiö and Ørvig 1951–1957) purporting to outline the foundations of

the lepidomorial theory has been cited many times in literature, both by the authors and by others (e.g., Jarvik 1948; Ørvig 1951, 1957; Stensiö 1961, 1962; Karatajute-Talimaa 1992, 1998; Reif and Richter 2001), although few, if any other than Erik Stensiö and Tor Ørvig, can have laid eyes upon it. The original manuscript survives as part of the Stensiö Archives at the Department of Palaeozoology, Swedish Museum of Natural History, Stockholm. This manuscript concerns the scales of edestids (holocephalan elasmobranchs) from the Permian of Greenland, which are divided into categories based upon characteristics of the vascular architecture, morphology, and inferred histogeny, and their relationship to the placoid scales of Recent elasmobranchs. The manuscript provides clarity in a number of contentious issues. It is clear that the foundation of the theory lies not with existence of lepidomoria, but in the study of edestid scales that exhibit evidence of growth through augmentation with what are effectively individual scales in their own right (Fig. 1G–K). Stensiö and Ørvig (1951–1957) attempted to compare these ''growing'' scales to the ''non-growing'' placoid scales of Recent sharks (Fig. 1A–F), and attempted to derive homology between the two. In doing so they used two criteria. First, they compared the number of vascular canals that supply the scales and, second, they compared the morphology of the scale crown in these and other groups. Using these as frames of reference for identifying homology, Stensiö and Ørvig (1951–1957) concluded that placoid scales are homologous not to one of the individual units that constitute the growing scales of Paleozoic sharks, but to a number of such units. (Retrospectively, it is possible to determine that these points are also made both explicitly and implicitly by Ørvig [1951] and Stensiö [1961, 1962].) The formulation of such homologies is clearly pattern based and the basic comparisons are valid regardless of whether the developmental explanation of this phylogenetic pattern is correct. More intriguingly, in this original formulation of the lepidomorial theory, Stensiö and Ørvig (1951–1957) use the lepidomorial concept in reference to their basic unit of homology (vascular architecture). Therefore, and at least in its original conception, a lepidomorium does not refer to the hypothetical developmental units referred to by Stensiö (1961, 1962), and there is little to distinguish the meaning of Ørvig's odontode concept from this early conception of the lepidomorium. It is perhaps because of this changed meaning of the lepidomorial concept that Ørvig erected the odontode concept, referring to the lepidomorial theory ''sensu Stensiö 1961'' (Ørvig 1977: p. 55), rather than sensu Stensiö and Ørvig (1951–1957), as he had earlier (Ørvig 1951, 1957). However, Stensiö and Ørvig (1951–1957) do also use both meanings interchangeably.

In contrast to the lepidomorial theory, the foundation of the odontode regulation theory lies with the development of placoid scales, and with the assumption that these scales represent the basic, irreducible unit of development in the dermal and visceral skeleton. It is an axiom of this theory that hard-tissue units (odontodes in the sense of Ørvig 1977) comparable in structure to placoid scales can be inferred to have developed in a directly comparable manner. This axiom is supported by Schaeffer's (1977: p. 26) argument that ''When the morphogenetic parameters for a particular organ or structure have been established through experimentation in living forms, and when no significant deviation from these parameters has been found, we may postulate that the morphogenesis of homologous adult structure occurred in extinct forms in the same way.'' Thus, in contrast to the pattern-based lepidomorial theory, the odontode regulation theory is process based.

This difference in approach has significant implications for the evolutionary patterns and processes perceived by the two theories. For instance, patterns of concrescence identified by the lepidomorial theory are evolutionary patterns, whereas patterns of differentiation observed through the odontode regulation theory are ontogenetic patterns. Thus, in consideration of debate over whether the lepidomorial and odontode regulation theories are synonymous (in whole or in part, e.g., Karatjute Talimaa 1998) or direct competitors (Reif 1982a; Reif and Richter 2001), we may conclude that neither situation obtains. Although both theories draw upon the same data set,

they address this data set in different ways. Indeed, it would appear that conflict with the lepidomorial and odontode regulation theories is, to an extent, unnecessary and the two theories have the potential to be complementary, collectively constituting a universal theory of the evolution of development of the vertebrate dermal and oral skeleton.

However, the two theories do clash, and this stems from the implicit assumption in the lepidomorial theory that ontogenetic and phylogenetic patterns equate; i.e., phylogenetic concrescence results from ontogenetic concrescence. This assumption is based partly on observations of homology, using the vascular system and oral morphology of teeth and scales as a frame of reference, and partly on the understanding that a *scala naturae* perspective of vertebrate phylogeny is characterized by a motif of skeletal reduction and assimilation. Given that there is no sclerochronological record of concrescence in the mineralized tissues of such dermal elements, Stensiö and Ørvig (1951–1957) were led to the conclusion that concrescence must have occurred ontogenetically at a stage prior to initial mineralization. Reif's (1973, 1974, 1978a, 1982a) attempted refutation of this hypothesis is flawed on two counts. First, his observation that placoid scales develop from individual uniform dental papillae is a corroboration of Stensiö's (1961: p. 243) own observations in the formulation of the lepidomorial theory. However, it must be conceded that Stensiö's argument, that the fusion of hitherto distinct dental papillae is obscured through phylogeny such that they cannot be observed in Recent elasmobranchs and holocephalans, effectively protects the hypothesis from falsification. Second, and more importantly, Reif failed to address the data on which the inference of ontogenetic concrescence was based, i.e., the inference of homology, as well as the use of vascular architecture as a criterion for tracing homology, within the dermal or visceral skeleton.

The odontode regulation theory requires rejection of the lepidomorial theory on two counts. First, unless it can be demonstrated that there is no level of homology below that of the odontode, the attempts of the odontode regulation theory to articulate and explain the evolution of teeth and scales are at best incomplete and at worst entirely spurious. Second, the use of vascular architecture as a means of tracing homology throughout the dermal and visceral skeleton, independently of the effects of both ontogenetic and phylogenetic concrescence and differentiation, provides an independent test of the odontode regulation theory, a test that the theory fails.

Thus, it is imperative that the relationship of the lepidomorial and odontode regulation theories is resolved such that a single universal theory of the evolution of development and patterning in the vertebrate dermal and oral skeleton can be achieved either through amalgamation or through rejection of one or both theories. To this end, the assumptions underlying these theories must be evaluated. Although these have been perennial questions in the study of the evolution of the vertebrate skeleton, recent advances in developmental biology and developmental genetics have begun to reveal the underlying basis of patterning and morphogenesis, and these data will be used in the evaluation of the lepidomorial and odontode regulation theories.

Before the implications of these experimental data are used to test the lepidomorial and odontode regulation theories, however, it is pertinent to note that these experiments are largely restricted to rodent dental development, and it is right to question how appropriate they are to understanding skeletal vascular patterning and morphogenesis in the teeth and scales of lower vertebrates. For instance, Smith and Coates (1998, 2000, 2001) have argued that the divergence of dermal and oral skeletal systems is both ancient, preceding the origin of jaws, and permanent. Thus, we might not expect tooth development in mammals to tell us very much about dermal scale development in, for example, Paleozoic lungfish. Furthermore, mammalian teeth exhibit a number of characteristics that are exclusively mammalian. Thus, we might also expect that mammalian tooth development is of little relevance to understanding tooth development in any other vertebrate. However, there is good reason to assume that these data do provide an adequate test of the lepidomo-

rial and odontode regulation theories. First, both theories have been applied throughout the dermal and oral skeleton of all vertebrates, including mammals. Further, mammalian teeth and the teeth and scales of other vertebrates exhibit precisely similar evolutionary patterns of morphological, numerical, and topological change, and are composed of homologous tissues that are arranged and develop in the same way. Finally, there is a compelling argument in favor of the ready applicability of mammalian tooth development to an understanding of dermal and oral skeletal development among a wide range of vertebrates. This centers on the fact that the early stages of tooth morphogenesis exhibit a striking comparison to other epithelial-appendage organogenic systems such as scale, hair, kidney, limb, liver, lung, mammary gland, and sweat gland. This comparison extends beyond morphological similarities in development, such as mesenchymal condensation and the thickening and folding of epithelial sheets (Krejsa 1979), to commonality of signaling and receptor molecules, transcription factors, cell adhesion, and extracellular matrix molecules that participate in the regulation of development (Thesleff et al. 1995; Chuong et al. 2000b; Peterková et al. 2000). Hence, the defective function of such molecules has been implicated as a causative role of multi-organ impaired development in such congenital syndromes as ectodermal dysplasias (Priolo et al. 2000; Thesleff 2000). Despite extreme conservatism, there are rare examples where the causative effects of such human syndromes have different effects in other vertebrates. For example, *cbfa1* loss of function in humans results in cleidocranial dysplasia syndrome, where bone is hypoplastic and patients develop supernumerary teeth (oligodontia [Mundlos et al. 1997]). In mice, however, *cbfa1* loss of function results in complete failure of bone development and in hypodontia, where tooth development is arrested at cap stage (D'Souza et al. 1999; Inohaya and Kudo 2000 have reported a similar function of *cbfa1* in teleost development). Such rare examples notwithstanding, it would be extremely surprising if the regulatory networks controlling tooth patterning and morphogenesis in mammals were significantly different from tooth and scale development in other vertebrates. Thus, we may follow Schaeffer's (1977) axiom inferring development in extinct organisms by comparison to generalism of development in extant organisms.

Testing the Lepidomorial and Odontode Regulation Theories

Experimental Data on Vascular Development.— Considering the clinical implications, it is quite astonishing how little is known about the development and architecture of the vascular system in the teeth of vertebrates. Most studies of the development of dental vasculature are restricted to mammalian teeth, and data are largely limited to inferences based upon comparing late fetal and adult phenotype. Lepkowski (1901) described the condition of the vasculature in the tooth germ of a seventh-month fetus. He was able to discern the branching of the inferior alveolar artery to each tooth germ, where each branch entered a tooth germ via the base and extended through the basal odontoblastic membrane to reach the forming dentine via a plexus of branching capillaries. Lepkowski observed that the vasculature varied according to tooth type such that there was a direct correlation between the number of vessel-bundles and the number of tooth cusps, giving the impression that the tooth had developed from a corresponding number of distinct units.

The most comprehensive data on vascular development during odontogenesis are based upon incisors and molars of rats (Bernick 1960, 1962; Yoshida 1991; Yoshida and Ohshima 1996) (Fig. 2). Yoshida (1991) concerns the development of the vascular architecture within the dental papilla from E18.5 (E = embryonic day) to E22, representing the day before birth. Bernick (1960) details the development of the vascular supply from bell stage through to early stages of occlusal function (from birth to approximately one month after birth) of rat teeth, molar teeth in particular. Bernick (1962) describes the development of the vascular architecture from one month to one year from birth. Yoshida and Ohshima (1996) detail the development of the peripheral capillaries and their relationship to odon-

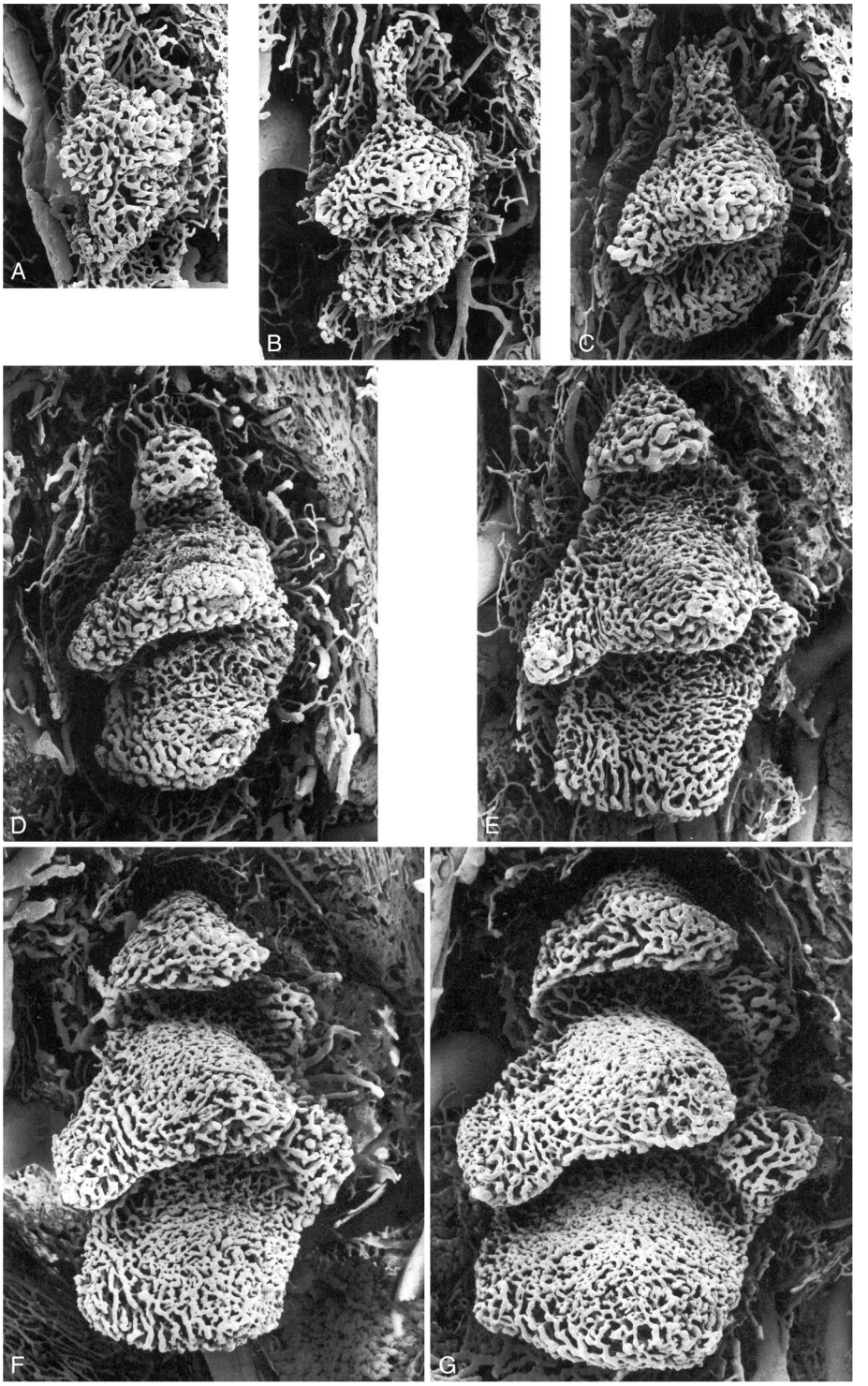


FIGURE 2. Development of vascular architecture of Wistar rat, from A, E19; through B, E19.5; C, E20; D, E20.5; E, E21; F, E21.5; to G, E22. All figures reproduced from Yoshida 1991. Reproduced with the permission of the author and publisher, Springer-Verlag.

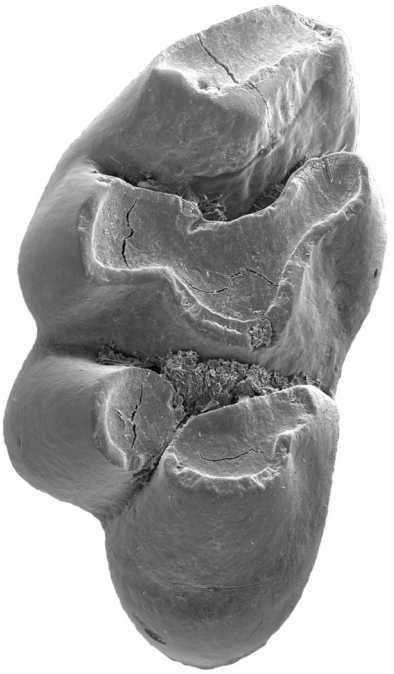


FIGURE 3. First maxillary molar of Wistar rat for comparison to the developing vasculature in Figure 2.

toblasts at the beginning and termination of dentine secretion.

The final morphology of the dental papilla is established at E22, by which time the pulp possesses five horns that correspond to cusps on the occlusal surface of the tooth (Fig. 3 is first maxillary molar from a four-week-postnatal Wistar rat for comparison—note that the cusps are heavily worn). However, at E18.5 there is a single horn that includes an irregular network of vascular canals. Subsequently, the distal horn develops (E19) with an associated cluster of irregular blood vessels that extend from the medial horn (Fig. 2A); there is also a mesial extension of blood vessels extending from the central horn that develops into a prominent vascular network by E20 (Fig. 2C). At this stage, the vasculature associated with the existing horns has become more regular and denser, through the sprouting and looping of capillaries. Vasculature associated with the disto-lingual horn development has begun by E20.5 (Fig. 2D), and the mesio-lingual horn vasculature by E21 (Fig. 2E). Vascular supply to each pulp horn exhibits a stereotypic pattern of development from an irregular network that grows through sprouting and loop formation, followed by an increase in the diameter of the blood vessels at the top of the horn, and a subsequent decrease in diameter associated with the development of the dental papilla. By E22 (Fig. 2G), the vasculature associated with each pulp horn is fully developed and consists of a dense and flattened network of thin vessels. The vascular network in the central pulp horn also exhibits evidence of sprouting at this stage, associated with the invasion of the vasculature into the odontoblast layer.

At the bell stage (at birth), small-caliber vessels can be observed within the dental papilla in thick histological sections, branching from the main vascular trunk to enter the tooth germ from below. These vessels divide within the core of the connective tissue, limited peripherally by the position of the future pulpal-odontoblastic border. By postnatal day 5, the developing teeth have reached appositional stage where both enamel and dentine are deposited in the crown. Within the dental papilla, the vessels are mostly orientated toward the cusp(s), but peripherally, fine-caliber vessels are observed. From base to crown, the peripheral limit of the terminal capillary branches progresses from the basal surface of the odontoblasts, through the odontoblastic layer such that they reach the developing dentine in the cuspal region. By postnatal day 15, the roots of the first premolar have bifurcated such that there are vessels passing distally, coronally, and into the cusp tips, where the vessels are profusely branched. The upper first and second molars are in functional occlusion by postnatal day 30, by which stage both the caliber and degree of branching have increased dramatically. By this time, the arterial branches of all the vascular canals pass through the odontoblastic layer to form a continuous capillary network in direct apposition to the predentine. This relationship starts to change at approximately four months, when a non-uniform retreat of the terminal capillary branches to the odontoblastic-pupal border is initiated, beginning in the cuspal area. By eight months, the terminal capillary plexuses have all withdrawn to the odontoblastic-pulpal border. Dentine deposition continues, and

the reduced volume of the pulp cavity results in convolution of the blood vessels, which are significantly reduced in number and of coarser caliber. The architecture of the pulp cavity is also reduced to a series of coarse channels that surround the remaining blood vessels. Advance and retreat of the vascular network relative to the odontoblasts is positively related to the activity of the odontoblasts (Yoshida and Ohshima 1996).

Experimental Data on Dental Patterning and Morphogenesis.—Although a significant time period has elapsed since Reif's main work on tooth and scale morphogenesis, we remain in a position where little is known regarding the regulation of morphogenesis in the dermal skeleton. In contrast, there has been an explosion in our understanding of molecular basis of patterning and morphogenesis of teeth, and this can be used specifically to test hypotheses of concrescence versus differentiation in the origin of complex heterodonty in early mammal evolution.

The earliest stages of tooth development are marked by thickening of the epithelium and by condensation of mesenchyme that has been demonstrated to be of neural crest origin in mouse (Lumsden 1984, 1987, 1988) and amphibian (Chibon 1966, 1967, 1970; Cassin and Capuron 1979). A series of epithelial-mesenchymal interactions ensue in which mesenchyme induces oral epithelium to proliferate, which in turn induces the proliferation of dental mesenchyme and the development of the dental papilla, which induces dental epithelium to form an enamel organ including preameloblasts; the preameloblasts induce differentiation of cells of the dental papilla into preodontoblasts and, ultimately, odontoblasts that induce preameloblasts to differentiate into ameloblasts, which synthesize and deposit enamel and induce odontoblasts to synthesize and deposit dentine (see, e.g., Lumsden 1987). The roles of epithelium and mesenchyme in tooth development have been extensively studied (Butler 1995; Thesleff et al. 1995), but the source of the initial inductive signal remains equivocal. In particular, *Pax9* expression has been implicated, as it specifically marks the mesenchymal regions of all teeth prior to any morphological manifestation of development (Neubüser et al. 1997), and *Pax9*-deficient mice lack all teeth (among other developmental defects [Peters et al. 1998]). Furthermore, temporal changes in *Pax9* expression can now be integrated with classic studies demonstrating the relative roles of oral epithelium and mesenchyme in murine tooth initiation (Kollar and Baird 1969; 1970; Kollar and Mina 1987, 1991; Lumsden 1988). These experiments demonstrated that initially (E9–11) oral epithelium has the potential to induce tooth formation, after which time the inductive potential is transferred to the underlying mesenchyme. These observations can be correlated with the results of tissue-recombination experiments, which indicate that until E11.5 epithelial signals are required to maintain the expression of *Pax9* in mesenchyme (Neubüser et al. 1997). The spatial control on *Pax9* mesenchymal expression appears to be controlled by the antagonistic effects of Bmp4 and Bmp2 on the inducing activity of Fgf8. Thus, Neubüser et al. (1997) have proposed that *Pax9* is induced only at sites in which Fgf8 is expressed in the overlying epithelium and where Bmp4/2 signaling does not interfere with the *Pax9*-inducing activity of Fgf8.

Tooth shape itself is dictated by the morphology of the dental epithelium and, thus, tooth morphogenesis is effectively regulated by the controls on epithelial growth and differentiation (Fig. 4). Initial development of tooth buds in the epithelium is associated with the appearance of transient signaling centers in the epithelium whose formation appears to be regulated by mesenchymal signaling (Keränen et al. 1998). Although the life history of these signaling centers is poorly understood, Bmp4 (Vainio et al. 1993; Bei and Maas 1998) and Activin βA (Ferguson et al. 1998) have been implicated in the initiation of bud formation; signals in all four signaling-molecule families are expressed by the signaling center. Subsequent growth of the dental epithelium into a caplike structure occurs through invagination about its tip such that the lateral margins of the developing epithelium extend into the mesenchyme to surround the developing dental papilla. This transition is controlled by a second signaling center, known as the primary enamel knot; this knot

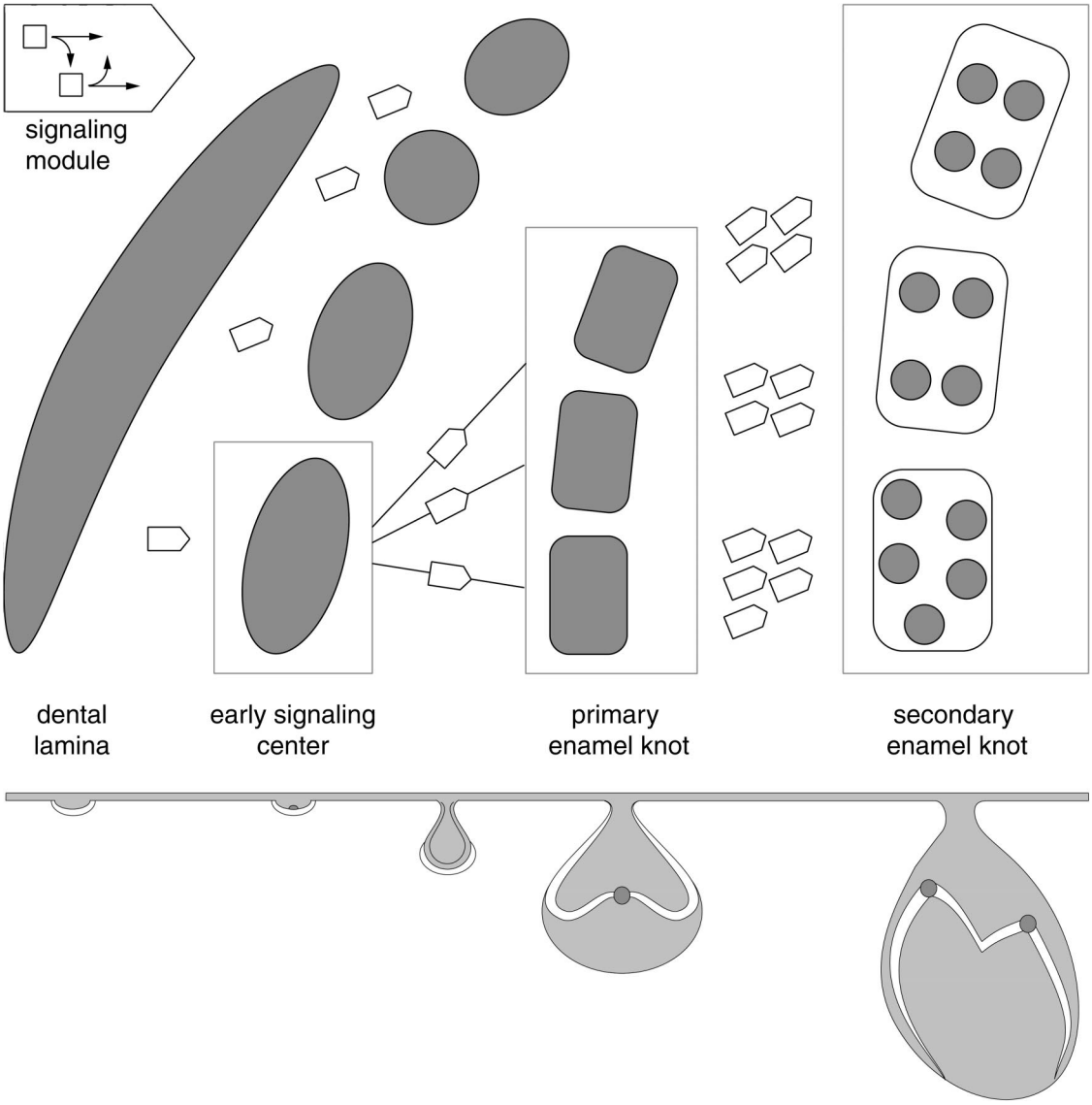


FIGURE 4. Diagrammatic representation of the sequence of segregation of the primordial dental lamina into a series of discrete primordia through the action of a cascade of patterning centers that are ultimately responsible for tooth phenotype. After Jernvall and Thesleff 2000.

develops at the site in the tooth bud from which folding of the epithelium begins and is important in regulating the ultimate gross morphology of the tooth (Fig. 4). Subsequent growth and folding of the epithelium is controlled by a third generation of signaling centers, the secondary enamel knots, which are responsible for the development of species-specific characteristics of dental morphology. The ''secondary'' enamel knots appear in sequence in cap to bell-stage developing teeth and consistently precede and predict the site of initial mineralized expression of cusps (Fig. 4). As the epithelium grows from the cusps down, the earlier the development of the cusp, the larger it is likely to be. Thus, cusp development is initiated sequentially in an order that will ultimately reflect decreasing relative height in the fully developed tooth.

Both generations of enamel knots appear to direct the differential growth and folding of the epithelium through the control of cell pro-

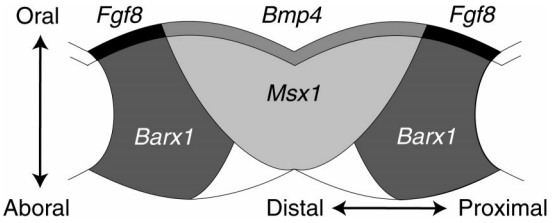


FIGURE 5. Schematic representation of the expression domains of *Barx-1, Msx-1, Bmp-4,* and *Fgf-8*. In the developing mandibular arch of the mouse. After Tucker et al. 1998.

liferation by mitogens, including members of the *Fgf* signal family (Kettunen and Thesleff 1998) around the non-dividing cells of the enamel knot. In vitro studies of the effect of *Bmp4* beads upon isolated dental epithelium (Jernvall et al. 1998) have implicated *Bmp4* in both the induction and the demise of enamel knots.

Because a common suite of genes is involved in the development of all cusps, it is unlikely that cusp-specific locational information determines the identity of specific cusps (Keränen et al. 1998). Rather, the sequential inception of cusps is envisaged as the product of a patterning cascade wherein differences in tooth morphology arise solely from heterochronic patterns of cusp initiation (Weiss et al. 1998). Further, it has been considered that all teeth in a dentition are serial homologs (Stock et al. 1997), and differences between specific teeth in a dentition arise from local modifications in the expression patterns of shared developmental regulatory genes. This is supported by evidence of homeotic changes across tooth classes, such as the molarization of premolars in horses (Butler 1978; see also Butler 1967). However, the significance of such changes is difficult to determine in the absence of data on their underlying basis. Recently, this view of teeth as serial homologs has received experimental support from a study in which transformation of tooth identity from incisor to molar was achieved through *Noggin*-mediated inhibition of *Bmp4* signaling in the distal mesenchyme of murine mandibular arch (Tucker et al. 1998). *Bmp4* otherwise inhibits expression of *Barx1,* restricting it to proximal presumptive molar mesenchyme (Fig. 5), and the experimental inhibition of *Bmp4* resulted in a distal expansion of the *Barx1* expression domain, resulting in a relative transformation of mesenchymal identity from incisor to molar. This transformation is limited, however, to a narrow temporal window prior to E11. Furthermore, this study offers a refinement of the widely appreciated view that tooth identity is conferred by mesenchyme (Kollar and Baird 1969, 1970) by implying that neural crest cells in the mandibular arch are equally responsive to epithelial signals and, thus, are not prepatterned but are specified by contact with epithelial signals. This equates well with evidence that neural crest cells participating in the formation of the first branchial arch are derived from the midbrain and are not pre-patterned—in contrast to neural crest cells involved in the development of the other branchial arches, which are derived from the hindbrain and are patterned by members of the Hox family of homeobox-containing genes (Lumsden et al. 1991). Nevertheless, the first branchial arch does express a number of homeobox genes including *Msx1/2, Dlx1/2/3/5/6/7, Barx1, Otlx2, Lhx6/7* in distinct spatial patterns prior to morphological manifestation of tooth development. This has led to the suggestion of an odontogenic homeobox code (Sharpe 1995; Thomas et al. 1998; Thomas and Sharpe 1998; Tucker and Sharpe 1999) in which the dental classes are defined by spatial combinatorial expression of some of the homeobox-containing genes that are expressed in the developing jaw. Thomas et al. (1998) suggested that molar expression domains are patterned by *Barx1,* and by *Dlx1/2* in the upper molars versus *Dlx5/6* in the lower molars, and the incisor expression domain is defined by the expression of *Msx1/2.*

Discussion

Vascular Architecture and Morphology.—Although Stensiö and Ørvig (1951–1957; Ørvig 1951; Stensiö 1961, 1962) appear to have been unaware of the contemporary work on dental vascular development, dramatic comparisons can be drawn between their observations and inferences on placoid scales, and what is known of vascular architecture and its development in mammalian dentitions. For instance, detailed developmental studies corroborate,

rather than refute, Lepkowski's (1901) view that the correlation between tooth cusps and the more or less discrete vascular loops suggest that teeth develop from a number of discrete units. And if it were assumed, as did Stensiö (1961, 1962), that vascular canals provide a landmark for identifying homology that is independent of concrescence, the multicusped teeth of mammals would be homologous to a number of distinct teeth or scales in less-derived vertebrates (e.g., Ameghino 1884). However, data on the development of the vasculature (outlined above) raise several reasons for concern. First, the vascular architecture of teeth is extremely dynamic, both increasing and decreasing in its extent during development. Furthermore, the assumption that pulp cavity architecture faithfully reflects vascular architecture (Stensiö and Ørvig 1951–1957) is unfounded not only because of the dynamic nature of the vascular network, but also because the pulp cavity contains other systems such as nerve networks, odontoblasts, and the pulp itself. Finally, the different vascular loops develop interdependently, such that they bud successively in a serial cascade, rather than exhibiting separate developmental histories as might be expected of discrete developmental units. Data on the development of the vascular network itself indicate that there is reason to doubt the reliability of vascular architecture in identifying homology.

Data on the morphogenesis of the tooth itself reveal that morphology is conferred and established after the discrete identity of each tooth primoridium has been established, through a hierarchical series of patterning centers. Hence, the presumptive tooth germs of single-cusped teeth have equipotential to develop into multicusped teeth, at least within a narrow window of early development, and this identity is conferred by gene expression within the epithelial field, rather than by any innate clone-patterning. Unfortunately, no data on the vascular architecture of the homeotic shift from presumptive incisor to molar phenotype from Tucker et al. (1998) are available and, thus, it is not possible to test this null model. Nevertheless, the parallel sequential budding characteristic of largest to smallest tooth cusps and vascular horns indicate that the two are closely correlated. However, data on vascular development indicate that the development of the vascular architecture follows the establishment of tooth morphology, as determined by the final folding of the dental epithelium and the differentiation of the odontoblasts that the vascular network supplies. Further, the architecture of the vascular network is determined by the architecture of the pulp cavity, and subsequent changes in the vascular architecture occur in response to the narrowing of the pulp cavity, as well as to decreased activity of the odontoblasts. Thus, it appears most likely that the architecture of the dental vascular system is constrained not by independent patterning but by the morphology of the tooth itself; thus, it is not phylogenetically constrained and does not provide us with a means of discriminating homology independently of morphology, as required by the lepidomorial theory. With the rejection of its underlying scheme of homology, the lepidomorial theory collapses.

Ontogenetic Concrescence and Differentiation.– An understanding of the morphogenetic basis of tooth development provides a means of testing both Stensiö's use of morphology as a guide to homology in the composition of teeth and scales and Reif's assumption that teeth and scales develop through differentiation rather than a mechanism of concrescence, as argued by the lepidomorial theory. The data indicate that although multicuspid mammalian teeth do indeed develop from, and are patterned by, separate signaling centers (secondary enamel knots), they do so only after secondary differentiation of a coherent tooth germ. No existing ontogenetic developmental data can be interpreted in support of the view that complex teeth arose phylogenetically through the amalgamation of numerous teeth of simple morphology (contra Ameghino 1884, 1896, 1899; Bolk 1912; Kükenthal 1893; Röse 1892; Stensiö 1961). Instead, the cusps within the developing tooth arise as the result of a patterning cascade of control centers that ultimately direct the position, and timing, of both onset and offset of development. Weiss et al. (1998; Zhao et al. 2000) have gone so far as to argue that although tooth cusps can be homologized within and between taxa, the lack

of specific genetic coding for their development is sufficient to cast doubt on the underlying basis of their homology.

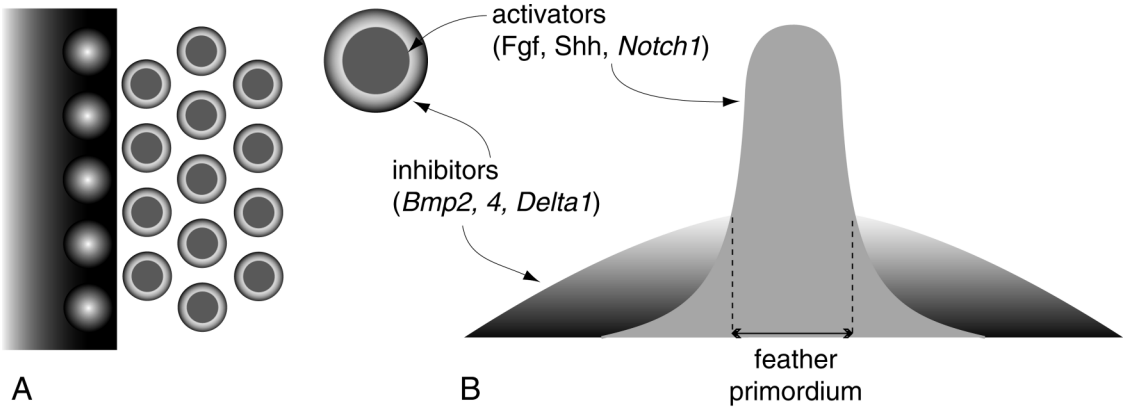
Given that tooth development—from the initial development of the dental lamina, through its patterning and division into distinct tooth classes and, ultimately, patterning of the specific teeth—is a process of progressive differentiation (a point emphasized by experimental division of tooth germs; [Glasstone 1952; Coin et al. 2000]), there does not appear to be any scope for a mechanism of ontogenetic concrescence. This process supports the axiom of the odontode regulation theory that assumes that changes in morphology are achieved through the differentiation of tooth germs. Indeed, on this basis it is possible to reject the implicit axiom of the lepidomorial theory, that all change occurs through ontogenetic concrescence, as well as the principle that ontogenetic concrescence is possible.

Teratological examples of putative dental concrescence, (concrescence, connation, double teeth, fusion, gemination, incomplete dichotomy, odontopagy, and synodonty) cover a multitude of types, from teeth that are fused together solely by cementum or by their roots, to, more rarely, teeth with fused crowns (e.g., Smith et al. 1953; Hitchin and Morris 1966; Miles and Grigson 1990; Law et al. 1994; Pavlica et al. 2001). There is considerable debate over their etiology in the literature, though it would appear that the most substantive examples result from the failure of differentiation of dental papillae, rather than from the concrescence of differentiated papillae (although there is some evidence of herniation of enamel organs in closely spaced developing teeth, resulting in connate teeth that are partially joined by the enamel layer but maintain distinct pulps and remain recognizable as distinct teeth). This finding is in accord with the observation that examples of ''concrescence'' do not cross the primary dental divisions in mammals.

Phylogenetic Concrescence and Differentiation.– Even though concrescence, as an ontogenetic developmental pattern, can be rejected, this does not preclude the possibility of concrescence in a phylogenetic context. However, before the question of how such patterns can be constrained, the issue of how a pattern of concrescence could be produced through ontogenetic developmental mechanisms that preclude ontogenetic concrescence will be explored.

Given that the differentiation of the dental lamina, into the stereotypical tooth suites of incisor, canine, and molar, is progressive, the only conceivable mechanism of (evolutionary) concrescence is through the lack/failure of inhibitory process that underlies differentiation. In the model system, rodent teeth, spatial control on development is conferred by *Bmp2* and *Bmp4* inhibition of the *Pax9*-inducing ability of *Fgf8.* Thus, evolutionary concrescence of otherwise distinct dentitions could occur through the absence of *Bmp2/4* expression. Such a mechanism has been demonstrated in patterning of another epithelial-appendage organogenic system, the feather array (a particularly appropriate analogy for squamation patterning). Feather primorida are induced and patterned by the antagonistic effects of *Bmp2/4* on *Fgf4* (Fig. 6A,B). Fgf4-soaked beads placed onto explants of the developing feather array result in a local breakdown in placode spacing and the development of fewer, larger feather primordia (Jung et al. 1998). Jung et al. (1998) and other authors (Peterková et al. 2000) interpret this as fusion of placodes, but in ontogenetic developmental terms, it is a failure of differentiation that provides a mechanism for patterns of concrescence apparent from comparative phenotypes at the intra- or intertaxon level.

The question of how to distinguish whether loss (differentiation) or fusion (concrescence) best explains phylogenetic patterns in Recent and/or extinct organisms is both old and problematic. One of the best examples concerns the identification of homologies in the evolution of dermal bone patterns in the skull roofs of osteichthyans. Homologous skull roof bones are identified by their relationship to adjoining bones whose homologies can similarly be constrained. Additional lines of evidence can be marshaled, including the relationship of individual bones to lateral line canals or grooves, a link that is apparently supported by evidence that developing neuromasts of the lateral lines actually induce the development of dermal



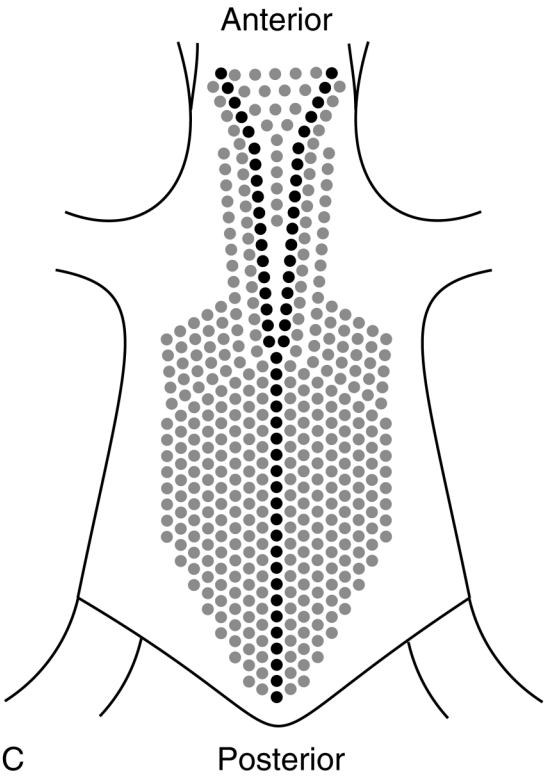


FIGURE 6. A, Feather placode development is initiated by a mesenchymal signal (graduated background) that induces *Shh* and *Fgf-4* expression (gray circles in foreground). Placodes subsequently express *Bmp-2* and *Bmp-4*, leading to inhibition of placodal fate in the surrounding cells. B, Hypothetical model of the signaling proteins based upon a reaction-diffusion model of feather placode development. The antagonistic effects of the long-range inhibitors (Bmp-2, 4, Delta-1) and short-range activators (Fgf, Shh, Notch-1) are dose dependent. In the center of the placode, activators are at peak concentration and override the effect of the inhibitor, resulting in a feather primordium. After Hogan 1999. C, Pattern of feather buds in the dorsal skin of the chick, the black dots represent the initiator or pioneer row that forms first in development. After Wolpert 1998.

bones (Allis 1888; Pehrson 1922; Devillers 1947). Association of dermal bones with characteristics of the neurocranium (Westoll 1938, 1943; Romer 1941, 1945; Parrington 1967; Graham-Smith 1978) as well as the functional roles of differing elements (Thomson 1993) have been cited as sources of phylogenetic data that can help constrain homology of the different bony plates that constitute the skull roof. Nevertheless, despite the many and varied potential landmarks and guides that may assist in constraining homology, the increase or decrease in the number of dermal elements forming the skull comes down to the same old problem. That is, in the example of a numerical decrease, did two (or more) plates fuse together, or has one plate been suppressed and its territory invaded by an adjacent bone (or bones)? Jardine (1969) wrestled with this problem and outlined the different approaches that may be taken in attempting to resolve between phylogenetic loss and fusion. For instance, we may consider the development of dermal bone patterns within a well-constrained phylogenetic context (Fig. 7A,B). However, we are never in possession of a complete phylogenetic series, and the discovery of additional intermediate forms is likely to upset any hypothesis of phylogenetic loss or fusion. This obtains regardless of whether hypotheses are formulated within an ancestor-descendent framework or composed from reconstructed character states of hypothetical common ancestors in a cladistic framework.

As Jardine (1969) argues, this difficulty might be resolved if phylogenetic change is considered not in terms of sequential changes in adult morphology, but as modifications in ontogenetic processes. Thus, we might only consider phylogenetic fusion should there be evidence of fusion in an ontogenetic sequence (Fig. 7C). However, this shifts the balance of evidence required such that the burden of proof lies with fusion, and loss (and hence differentiation) supersedes fusion as the preferred explanation in all instances where such proof is not forthcoming. This is problematic because loss is concluded even in the absence of evidence. Potentially more problematic, however, is the assumption that changes in the ontogenetic program are more prevalent at late, rather than early, developmental stages. This ''biogenetic law'' (Haeckel 1866) has famously been refuted on the basis that changes in development most often appear to have been effected through the alteration, rather than in the superseding, of developmental programs (Sedgwick 1894; de Beer 1958; Gould 1977). Thus, the ontogenetic-phylogenetic link still cannot preclude the possibility that progenetic, peramorphic changes in the timing of fusion of dermal bones during development will be misinterpreted as loss and differentiation in the absence of proof of fusion.

In practice, many authors have simply adopted an axiom that reduction in the total number of cranial bones reflects either loss (Watson 1921; Moy-Thomas 1938; Parrington 1949, 1956, 1967; Romer 1945) or fusion (Stensiö 1921, 1947; Säve-Söderbergh 1933, 1935, 1941; Jarvik 1944, 1948, 1950, 1952). Westoll (1938, 1943, 1949) took the approach that although phylogenetic fusion may occur, it did so only within the subsets of lateral-line-bearing bones or bones that do not encompass lateral lines.

Clearly, it is extremely difficult to reconcile whether phylogenetic differentiation or concrescence is responsible for a decrease in the number of skeletal elements. This is vividly apparent from the example of osteichthyan cranial bones where, in almost all instances, the individual elements can be determined as homologs of elements of cranial bones in other individuals and other taxa. Even in mammalian teeth, where individual teeth are both morphologically and positionally distinctive, identifying precise homologies where there has been an increase or decrease in the number of teeth, and thereby reconciling phylogenetic differentiation and concrescence, can be impossible (Bateson 1892, 1894; Van Valen 1964, 1982). Thus, the situation in much of the remainder of the dermal skeleton, where individual elements are indistinguishable morphologically or topologically, ensures that discussion of patterns such as fusion or loss are entirely vacuous. An example of such an intractable problem is provided by a developmental study of feather patterning. Feathers, like teeth and scales, develop as epithelial appendages and,

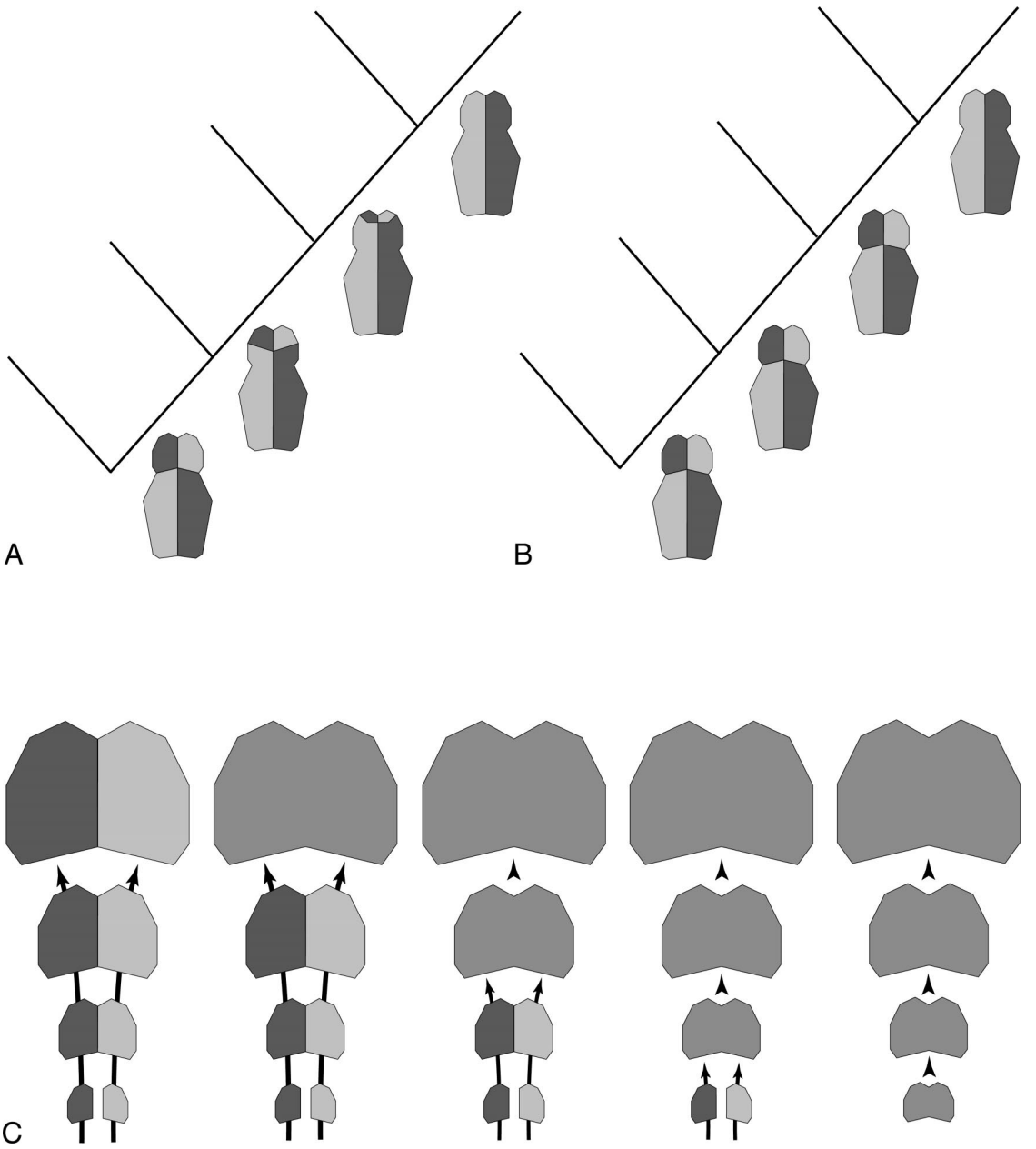


FIGURE 7. Reconciling between evolutionary concrescence and differentiation in a hypothetical arrangement of skull roof bones. A, A phylogenetic sequence that suggests ontogenetic concrescence/fusion. B, A phylogenetic sequence that suggests ontogenetic differentiation/loss. C, A paedomorphic sequence of taxa in which the concrescence/fusion of two dermal plate primordia occurs progressively earlier in ontogenetic development.

like scales, they are also a manifestation of the dermoskeleton. Feathers also exhibit serial homology, in that the individual feathers are not distinguishable on any criterion. Research into the underlying basis of feather patterning demonstrates that individual feathers have no ''individuality.'' Like rodent teeth, feather patterning is controlled by antagonistic activation/inhibition mechanisms, with feather placode induction involving *Bmp2, 4,* Delta1 acting as inhibitors, and *Fgf*'s, Shh, Notch1, Noggin, Follistatin operating as activators (Fig. 6A,B) (Crowe et al. 1998; Jung et al. 1998; Viallet et al. 1998; Jiang et al. 1999; Chuong et al. 2000a).

These act randomly within an initially uniformly competent feather field and their activity is such that the resulting pattern conforms to close packing. Thus, the precise (and, to a degree, the relative) position of a feather primordium, or interprimordium, is an issue of probability rather than predetermination (Jiang et al. 1999). The limited available data on the underlying basis of scale patterning (Quilhac 2000) suggest that this system is comparable to patterning of the feather array, and therefore these conclusions have broad relevance.

Thus, even when the number of elements constituting an array of feathers or a squamation of scales remains constant, the absence of distinguishing characteristics of individual elements, in terms of either morphology or topology, precludes the possibility of identifying homologous elements between one individual, or taxon, and another. Attempts to discriminate between phylogenetic patterns of concrescence or differentiation among serially homologous elements are therefore entirely futile. However, before we all give up, it is worth examining the nature of conclusions such as phylogenetic concrescence and differentiation. Other than in the context of ancestor-descendent relationships, the identification of ''phylogenetic'' concrescence or differentiation has no real meaning, because they do not describe actual evolutionary events but merely articulate the nature of the relationship between one condition and another. And, given the intangible nature of ancestor-descendent relationships, we should not, therefore, be despondent that we cannot reconcile phylogenetic concrescence and differentiation.

Homology.—A significant problem is inherent in the concept of homology as it is applied to studying the evolution of development of the vertebrate dermo-visceral skeleton: precisely what is meant by the assertion that teeth and scales are homologous? Similarities of composition and development compose the data marshaled to support this, the ''odontode'' hypothesis. This is homology in the sense of the ''biological homology'' concept (Roth 1988; Wagner 1989), rather than in the historical or phylogenetic sense, as has classically been perceived by the term ''homolog'' since it was ''evolutionized'' by Darwin. Biological homologs are useful in terms of individualizing morphogenetic anatomical building blocks, and in attempting to reconcile why different organs with very different phylogenetic histories have such similar developmental backgrounds (Wagner 1999). However, biological homologs are of limited use if the objective is to trace the evolution, or the evolution of development, of a phenotypic structure through phylogeny, as it is here. Critically, biological homologs lack the phylogenetic constraint that identifies ''historical'' homologs as the ''same,'' rather than merely ''similar,'' in different individuals. Thus, stating that teeth and scales are the same (i.e., homologous) on the basis of their development is little more than a truism; as a theory it makes no predictions and implies nothing more than the formulation on which it is based. This stands irrespective of hypotheses contending that teeth evolved from dermal scales, for example, through co-option of a dermal scale cover that invaded the mouth (cf. Halstead Tarlo and Halstead Tarlo 1965), or through heterotopy (cf. Hall 1998).

Research into the underlying basis of these comparisons, traditionally considered ''serial homologs,'' has revealed that homology is entirely contingent upon the dynamic quantitative, temporal, and spatial interaction of various signaling factors. This has been offered as a counsel of despair by some developmental biologists who doubt that, in the absence of direct genetic control of morphogenesis, any such comparisons can represent true homologs (Zhao et al. 2000). However, we must remember the distinction between *explanans* and *explanandum* in our concept of homology. The operational criteria on which we propose homology have changed little since the concept was first formalized outside of an evolutionary context by Owen. A hypothesis of homology is the *explanandum,* the phenomenon that is to be explained; evolution provides the *explanans,* the explanation of the phenomenon. But evolution provides only one explanatory perspective on the phenomenon and development must provide the explanation of the ontogenetic mechanism that underlies the similarities and differences between proposed

homologs. When this explanation is not what was originally expected, this does not erase the phenomenon but suggests that our understanding of the mechanisms that underlie conserved similarity are not quite as universal as originally thought.

It is tempting to conclude from the relatively random nature in which the topological position of serially homologous elements are patterned that our inability to recognize homology within serially homologous elements is not simply a result of limitations in comparative anatomy, but a reflection of fact (cf. Jiang et al. 1999; Chuong et al. 2000a). However, the discovery that individually identifiable homologous elements have a common developmental basis in patterning and morphogenesis as serially homologous elements (that, by definition, lack individual identity), together with the recognition that identity can be conferred entirely epigenetically, demonstrates that homology is all about identity. Thus, as comparative anatomists, we are limited solely by our ability to individualize identity.

Toward a Universal Theory of the Evolution of Development of the Vertebrate Dermoskeleton and Dentition?

A single universal theory of the evolution of development of the vertebrate dermal and oral skeleton is possible. However, it is clear from the experimental data outlined above that such a theory does not lie in the direction of the lepidomorial theory. The ontogenetic development of the dermal and visceral skeleton follows a pattern of progressive differentiation and, thus, there is no scope for concrescence, other than in a phylogenetic context. The lepidomorial and odontode regulation theories concern homology only at a conceptual level—comparative analysis of an abstraction of structure, development, and patterning in teeth and scales. This is because in almost all instances, it is simply not possible to identify the same element in the squamation or dentition of different individuals or different taxa. And given the lack of homology of individual elements in the dermal and oral skeleton of most vertebrates, attempts to discriminate between patterns of concrescence and differentiation are futile and vacuous. An assertion that differentiation is a more parsimonious interpretation of phylogenetic patterns than is concrescence, as argued by the odontode regulation theory (Reif 1982a: p. 348), implies certainty and data where there are none. These problems notwithstanding, Reif's odontode regulation theory is close to a universal theory of the evolution of development of the vertebrate dermal and oral skeleton. However, Reif's ''differentiation theory can only explain changes in numbers of scales and teeth but not changes in number'' (Reif 1982a: p. 348), and a weakness of the theory lies in its inability to trace homology below the level of the odontode. The experimental data summarized herein indicate that the odontode regulation theory can be supplemented with the axiom that patterning, as well as morphogenesis, is achieved through differentiation. Thus, there is no homology below the level of the odontode. It is in many ways unfortunate that we cannot go further and attempt to explain changes in the number of elements constituting the squamation and dentition of vertebrates, but such subjects lie outside of the sphere of scientific enquiry. A universal theory of the evolution of development of the vertebrate dermal and oral skeleton should therefore be restricted in its remit to addressing ontogenetic development (cf. Reif 1980a) and its relation to phylogeny.

The Molecular Basis of Regulatory Patterning Mechanisms

Setting aside the characteristics of the basic patterning unit in the dermoskeleton and dentition, the odontode regulation theory also concerns the regulatory mechanisms responsible for induction, arrangement, and maintenance through ontogeny of skeletal elements within these skeletal systems, with varying degrees of success. Although Reif addressed the problem of how topological information may be conveyed in the developing squamation or dentition, he was unable to arrive at any satisfactory conclusions. Similarly, he made little advance in understanding the induction and establishment of squamations, although he undertook significant work on the establishment of dental patterning in sharks. One area in which Reif did make significant

headway was in developing a regulatory mechanism for the local spatial and temporal relationship between individual elements. The ''zone of inhibition'' model (Reif 1980a) became the central regulatory mechanism in the ''odontode regulation theory,'' and it holds that the development of individual teeth and scales is constrained by lateral ''zones of inhibition'' that preclude the development of new skeletal units in the vicinity of existing elements, both during initial development and, subsequently, in the regulation of patterning during replacement. This was developed from Reif's earlier work on tooth replacement (Reif 1976), squamation ontogeny (Reif 1974), and wound repair in the dermoskeleton (Reif 1978c). In the case of scales, Reif observed that the regular close-packing arrangement precluded development of additional scales unless new space was created over an above-the-normal interscale spacing, either through an increase in surface area of the dermis concomitant with volumetric growth of the animal, through shedding of old scales, or through wounding in which portions of the dermis were removed. In extant sharks, space in the squamation is taken up by new scales that develop between, and distinct from, those already present. However, in Paleozoic sharks, and many other groups, new space can be taken up through the augmentation of existing scales with new scales that either are attached to the side of or completely envelope the existing scales. The inhibitory field concept was developed to account for the available facts relating to the ontogeny of the dermal skeleton and dentition (Reif 1974, 1976, 1978c, 1980a). However, considering modifications to its timing extent and interactions with other mechanisms, such as shedding, Reif (1982a,b) extended the model as a mechanistic explanation for the differences between the universe of dermoskeletal and dental conditions encountered among living and fossil lower vertebrates. Although Reif did not speculate on the basis of such zones of inhibition, he suggested that they would function through diffusion from the developing and adult scale or tooth. Taking scales as an example, the radial extent of the inhibition zone relative to the radius of the scale structure determines the proximity of contemporaneous scales to one another, and new scales can be initiated only if portions of the dermis fall outside the perimeter of overlapping inhibition zones exerted by adjacent scales. This degree of complexity accounts only for the maintenance of squamations in which the component scales are of nongrowing type, as in modern shark scales. To account for growing scales, which is the most general condition met with in lower vertebrates, Reif (1980a) suggested that the extent and influence of zones of inhibition might degrade over time and, depending upon the ''half-life'' of the inhibition zone relative to the lifetime of the animal, growth of the squamation would keep pace with surface area increase in the dermis, through either scale augmentation (growing scales) in the case of a short half-life or the addition of discretely positioned scales in the case of a long half-life.

Reif's inhibitory zone model is entirely empirically based, and although it has yet to be tested with data other than those on which the model was originally based, it provides not only an excellent explanation of the available facts, but also a mechanistic explanation of how the universe of dental and dermoskeletal conditions encountered among fossil and living lower vertebrates might appear. How does this compare to the regulatory mechanisms underlying development in better-understood systems? As has already been seen, development of the chick feather array exhibits a number of very detailed parallels to tooth development. But many of the phenomena that Reif attempted to account for in the dermoskeleton and dentition of sharks and other lower vertebrates are the same as those classically addressed in experimental attempts to understand the establishment and regulation of the chick feather array during development. Thus, further comparison may prove insightful in assessing Reif's model of inhibition zones regulating scale and tooth patterning. Furthermore, data on the regulatory basis of development in the chick feather array may provide a new perspective on the dermoskeleton in areas where the odontode regulation theory is delimited, such as in terms of how positional information is conveyed during development

and in maintenance during subsequent ontogeny.

The pattern of induction of the overall feather array is quite different from scale induction in Reif's model system, living sharks. For instance, Reif's documentation of scale induction in carcharinid sharks indicates that all first-generation scales within a given region form simultaneously and are originally randomly arranged (Reif 1980b). Reif (1980b) contrasted this with the situation in the feather array, where feather buds first appear as a single dorsal longitudinal ''initiator'' row, or ''file,'' after which successive rows are added dorsolaterally (Fig. 6C). Subsequent work has demonstrated that the appearance of the initiator file is preceded in development by expression of a single solid strip of low-level *Fgf4* and *Shh* expression within the dermis, which is subsequently subdivided into a row of cell groups that exhibit high-level expression of these genes and, subsequently, of *Bmp2* and *Bmp4* in both the epidermis and mesoderm. The same antagonistic interactive role of these genes in delimiting the developing dentition has been replicated through the ectopic application of their transcripts and implicated in the developing feather array (Jung et al. 1998). *Shh* and *Fgf4* promote feather placode induction as short range activators, whereas Bmp's, emanating from the same point source, act as long-range inhibitors constraining feather bud shape and preventing induction of new, adjacent feather buds (Fig. 6A,B). Feather buds are induced and their size is regulated through the concentration-dependent interaction of activators and inhibitors such that over-threshold concentration of the activator (*Fgf4*) relative to inhibitor (*Bmp*'s) circumscribes the feather placode; the remaining area of below-threshold activator adopts the fate of an interbud area (Fig. 6A,B). Feather bud development is further constrained via cell-cell signaling molecules such as in the Notch-Delta pathway, and although the full repertoire has yet to be determined, as have precise roles of those already implicated, Crowe et al. (1998) have, for instance, demonstrated that *Delta1* both promotes feather bud development in the overlying ectoderm and inhibits placode fate laterally. Feather induction is ultimately constrained by a wave of competence that, within the primordial stripe, is at first concentrated at the posterior end and subsequently propagates anteriorly, and then laterally, allowing the cells to react to the activators; the timing and polarity of competence differs for different regions of the dermis.

Although there are clear parallels to the induction of complex deciduous tooth families, Reif (1980b) ruled out the relevance of the developing feather array to understanding squamation induction in sharks because of the difference between tightly regulated patterning in the chick and apparently topologically random induction of scales in carcharinids. It is not possible to test this comparison any further for lack of developmental data, but it is interesting to note that the condition in living sharks is quite unrepresentative of lower vertebrates (''fishes'') in general and is possibly unique. In all other groups of lower vertebrates with a dermal skeleton, and for which data are available, induction of the squamation begins with a row or field of pioneer scale primordia (Fig. 8A–D). Although the topology of the pioneer primordia varies, in many taxa it is the rows of lateral line scales, for example, in acanthodians (Watson 1937; Zidek 1985), sarcopterygians (*Neoceratodus forsteri* [Anne Kemp personal communication 2002]), basal actinopterygians (''palaeonisciforms'' [Schultze and Bardack 1987; Hutchinson 1973]), and teleosts (*Salmo* [Jollie 1984], cyprinids [McCrimmon and Swee 1967; Andrews 1970], *Brachydanio rerio* [Armstrong 1973; Sire et al. 1997]). Among the exceptions, scale row induction sweeps posterior to anterior with a ''<'' front (apex oriented rostrally) and either is initiated by the lateral line (e.g., *Pomoxis* [Ward and Leonard 1952]; *Aplodinotus* [Priegel 1966]), initiates as a mid-lateral rostro-caudal row independent of the lateral line (e.g., *Centrarchus* [Conley and Witt 1966]), or otherwise initiates with scales associated with fin bases (*Pomoxis* [Cooper 1971]). Variation notwithstanding, there is clear evidence of a common theme among lower vertebrates, bar living sharks, of scale induction beginning with a single pioneer row or field, as in the chick feather array. Indeed, just as regulation of the

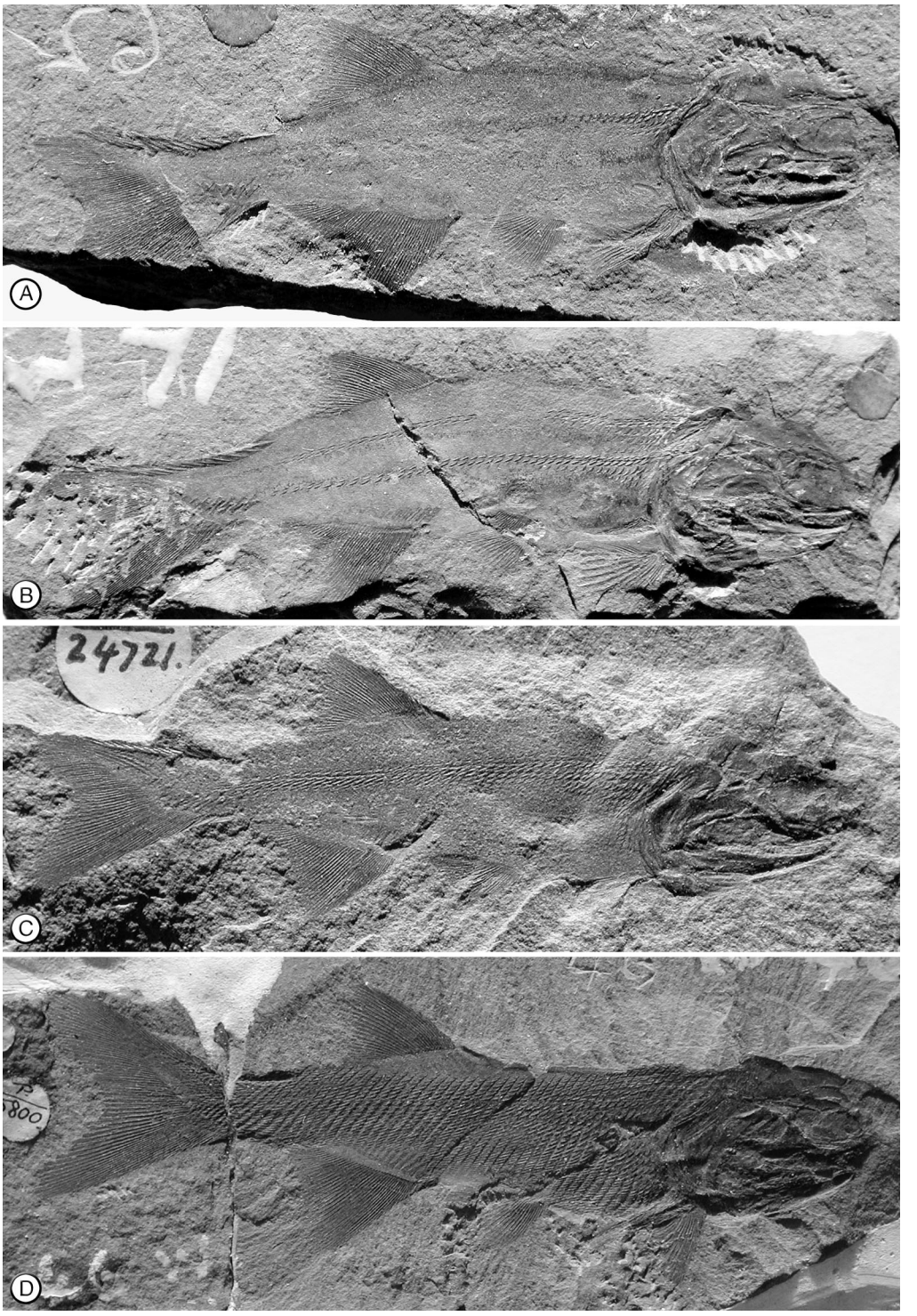


FIGURE 8. Squamation development in the Triassic actinopterygian *Brookvalia gracilis* Wade (basal crown-group actinopterygian, stem-group actinopteran). The specimens are reproduced at constant frame width (and, thus, different magnifications) such that they best convey the sequence of squamation development; note that the scales of both sides of the body are preserved within the same plane. Specimens from The Natural History Museum, London. A, A 42-mm individual exhibiting a single, partially developed paired row of scales flanking the main lateral line; NHM P15808; note that this image has been digitally reversed along horizontal axis to maintain an orientation consistent with the other figured specimens. B, A 52-mm individual exhibiting a single complete paired row, and

chick feather array is distinct in different parts of the body, patterns of scale induction appear to belie distinctly regulated body and fin squamation fields. Although there are very few data on squamation development in Paleozoic sharks, there is some evidence to suggest that the condition met with in living sharks is a derived peculiarity. Microvertebrate collections indicate that the earliest known chondrichthyans had an extensive dermoskeleton (Sansom et al. 1996), but most Paleozoic chondrichthyans known from articulated remains, for example, *Stethacanthus* (Lund 1985) and *Diademodus* (Zangerl 1981), almost entirely lack a dermoskeleton, except for scales in the head region and in association with the lateral line, i.e., those scale rows that appear first during development and are most likely to be retained upon reduction of the dermoskeleton during phylogeny. Although these taxa appear to be basal stem-holocephalans (Coates and Sequeira 2001) and adult primitive chondrichthyans were fully enveloped by dermal scales (Young 1982), *Stethacanthus* and its kin nevertheless provide a constraint on squamation ontogeny among basal chondrichthyans. Thus, at least plesiomorphically, it is likely that chondrichthyans also conform to a pattern of squamation development that is general for crown-group gnathostomes at the very least. The establishment of the main squamation in lower vertebrates as a whole therefore appears to be more comparable to the chick feather array than Reif (1980b) envisaged in his study of carcharinids alone.

Experimental manipulation of development in the chick feather array also provides insights into how positional information may be conveyed in patterning the squamation such that the correct scale morphology develops in the correct topological position. Heterotopic grafting of chick paraxial mesoderm and overlying ectoderm results in the development of a feather pattern that is characteristic of the orientation and axial level from which the graft was removed (Mauger 1972). This implies that there is an underlying patterning mechanism conferring positional information along the anterior-posterior axis during development of derivatives of paraxial mesoderm (dermotome). Axial patterning of sclerotomal derivatives of paraxial mesoderm such as the vertebral (endo)skeleton of amniotes, where positional and, thus, morphological identity is conveyed, is conferred by the Hox family of homeotic genes (Gaunt 1994; Burke et al. 1995). Recent in situ hybridization experiments have confirmed that some Hox transcripts maintain structural colinearity even after the dermatome-derived dermal cells are in position, in both chick and mouse (Kanzler et al. 1994, 1997; Reid and Gaunt 2002) (although there are differences between these taxa in terms of which Hox genes maintain structural colinearity). Structural colinearity of the dorsolateral dermis of chick has so far been explored in relatively few Hox genes, and among these only a small fraction have been observed to follow this rule (Reid and Gaunt 2002). Nevertheless, expression domains of at least one of these three (*Hoxb4, Hoxa7, Hoxc8*) is known to coincide with the transition between two different morphological compartments of spinal pteryla (Reid and Gaunt 2002).

The role of Hox genes in axial patterning has not been demonstrated among ''fishes,'' although they exhibit comparable, albeit condensed, expression boundaries in the zebrafish (Prince et al. 1998) that correlate to consistent patterns of axial innervation (Burke et al. 1995; Burke 2000). Further, the role of Hox paralogs in axial patterning of arthropods indicates that this is a symplesiomorphic character of bilaterians (Carroll 1995; Tabin et al. 1999). Intriguingly, phylogenetic constraint on their roles in development within the chordate lineage is conferred by *Branchiostoma*, where Hox genes are not expressed in paraxial mesoderm (Garcia-Fernandez and Holland 1994) and, thus, expansion of the role of Hox genes

←

the rostral end of three new ventrolateral scale rows; NHM P15806. C, A 58-mm individual exhibiting four or five complete scale rows, in both ventrolateral and dorsolateral positions, with the rostral portion of a number of additional scale rows; NHM P24721. D, An 82-mm individual with an almost complete squamation; NHM P15800.

in patterning the dermo- and axial skeletal systems must be a craniate or vertebrate synapomorphy (cf. Sharman and Holland 1998), occurring within the gnathostome stem lineage at the very latest (cf. Coates and Cohn 1998). This does not by any means provide the definitive answer to how positional identity is conveyed to the developing dermoskeleton, and many other regulatory genes must be implicated in constraining topologically dependent expression of the dermoskeleton, but it does go some way to providing an understanding of how topological information is conferred. In the case of the dentition, Hox genes are not implicated because their expression domains do not extend rostrally as far as the mandibular arch and, as has already been discussed, other regulatory gene families, such as Barx, Dlx, Lhx, Msx and Otlx have been implicated in providing spatial identity during dental development (e.g., Sharpe 1995), at least within mammals.

There are thus clear parallels between patterns of induction, development, and pattern regulation of the chick feather array and scale squamation of lower vertebrates, sufficient, indeed, to use the better-known feather array as a model for assessing the veracity of Reif's pattern regulation mechanism. Good evidence exists for a molecular basis to Reif's ''zones of inhibition''; the mechanics that underlie the phenomena that Reif described are more complex than he envisaged, however, and involve a number of regulatory mechanisms concerning the progressive restriction and refinement of originally uniform expression domains of a variety of signaling molecules, to eventually circumscribe the sites of primordial elements. Reif's implicit assumption, that the epithelium is uniformly competent at the outset and that periodic patterns self-organize from an initially random state, seems at best oversimplified and, at worst, unjustified. Although the initial expression domains may be uniform, they do not initially encompass the entire developing field, and they undergo progressive restriction before the cell in which the signaling molecules are expressed achieves competence (cf. Jung et al. 1998). Further, although periodic patterning appears to be self-organizing, this is true only to a degree. Jung et al. (1998) argue that the available evidence indicates that patterning is achieved in the manner envisaged by Turing (1952), through the effect of random interaction between multiple point sources of differentially diffusing activators and inhibitors. The overall patterning of the feather array is, nevertheless, tightly constrained by compartmentalization into distinct fields, in which induction proceeds only after achieving competence in a controlled and progressive pattern of induction.

The only molecular data on scale development are limited to regeneration (Quilhac 2000), but they nevertheless indicate that the same genes involved in induction and development of the initial feather array in the chick are also involved in the induction and patterning of replacement scales in the zebrafish. It is not so obvious how the chick model could be interpreted to account for patterns of growth akin to the growing scales of Paleozoic sharks and most other ''fish'' groups; this problem is particularly significant given that scale ''growth'' appears to be the plesiomorphic condition for the dermoskeleton (Donoghue and Sansom 2002). However, in this matter it should be remembered that scale ''growth'' is just a modified form of scale replacement in which the existing scale remains in place and the ''replacement'' scale adopts a position adjacent to the existing scale rather than a distinct position between existing scales. A model akin to Reif's (1980a) diminishing inhibition zone could be developed from the activation-inhibition model of feather array patterning to account for this phenomenon through increasing the relative concentration of the activator to inhibitor and, thus, expanding the zone of scale induction beyond the limits of the existing scale. This model would stand in contrast to the regular pattern of scale replacement in which a portion of the dermis falls outside the influence of inhibitors as a result of growth of the animal. Increased topological dominance of the activator could be achieved through increasing absolute concentration of the activator or decreasing inhibitor-dosage, and depending upon whether this effect was polarized or equant, scale augmentation would occur through marginal or areal growth.

Does the developmental model provided by the chick feather array provide a better frame-

work for understanding the evolution of the vertebrate dermoskeleton from a developmental perspective than does Reif's inhibition zone theory? This is not an either-or debate; Reif's theory is entirely empirically based and the main mechanisms that underlie it are also a grossly simplified view of the regulatory basis of feather array development. More appropriately, the model of feather array patterning and induction should be used as a predictive model in experimental analyses of squamation development in lower vertebrates. Initial forays into constraining the molecular basis of squamation and scale development have begun with the zebrafish (Quilhac 2000). This is an ideal model animal in which to test the veracity of the chick model in detail because many or all of the regulatory genes implicated in development of the feather array have already been cloned in the zebrafish. The relevance of this reaches beyond the understanding of dermoskeletal development to examining the phylogenetic distribution of regulatory gene networks responsible for patterning periodic elements and exploring the nature of evolution and homology within such networks.

Concluding Remarks

As mentioned in the introduction, this contribution has been restricted, almost exclusively, to testing established theories that seek to explain the evolution of development of the vertebrate dermal and oral skeleton. Thus, in common with these theories, it has addressed directly only the odontogenic component of the oral and dermal skeleton. Research into the molecular patterning controls on the development of the skeletogenic system remains at a relatively early stage and the regulatory gene networks have yet to be explored. However, what little is known (see, e.g., Opperman 2000 for cranial sutures; Quilhac 2000 for the only available data on patterning of elasmoid scales) suggests that such development is constrained by comparable controls; furthermore, many of the examples and data used in this analysis demonstrate that the same patterning phenomena encountered in the odontogenic system are also found in products of the skeletogenic system. Thus, we may extend the conclusions reached above to the skeletogenetic scleroblastic system, with the caveat that the odontogenic and skeletogenic systems are often independently patterned (judging from empirical evidence from the distribution of their products in living and fossil vertebrates [e.g., Westoll 1967]). And although both systems are ubiquitous in the dermal skeleton of the extinct groups of ''armored'' jawless vertebrates in which the skeletal system first evolved, the odontogenic and skeletogenic systems are, in large part, mutually exclusive in the dermoskeletons of living vertebrates (exceptions include the lower actinopterygians and lower sarcopterygians). Attempts to trace the evolution of development of the dermal and oral skeleton have, in the past, conflated these two scleroblastic systems. Future analyses must unravel the contribution of these two distinct systems and the relative influence that patterning of either system has upon the final skeleton.

The first attempts to test the applicability of patterning models based on other epithelial-appendage systems, such as teeth, feather, lung etc., on the patterning of the dermal skeleton have begun (Opperman 2000; Quilhac 2000). It will be interesting to see how similar the underlying basis of patterning and morphogenesis seen in scales is to that in their putative closest system, the oral skeleton, as compared to other organ systems within the epithelial appendage family (Chuong 1998). Wider taxonomic analysis of model systems lies at the heart of our attempts to unravel the evolution of developmental systems. But it is only in combination with further exploration of the diversity of organogenic systems within the epithelial-appendage family that will we begin to discover whether their similarity in development results from conservation (e.g., genetic piracy Roth 1984) or more simply, a conservatism in developmental programs.

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