Hall, B.K., and J. Hanken. 1985. Foreward to G.R. de Beer, The Development of the Vertebrate Skull, pp. vii-xxviii. University of Chicago Press, Chicago.

FOREWORD

THIS volume commemorates the approaching fiftieth anniversary of Sir Gavin Rylands de Beer's *The Development of the Vertebrate Skull*, originally published in 1937. In an age when many scientific works are virtually outdated as soon as they appear in print, its republication is indeed a testament to the tremendous impact de Beer's book had on the field of evolutionary vertebrate morphology, and to the high regard in which it continues to be held.

It is a truly monumental work: 515 text pages supplemented with 143 plates, 205 entries in the genera index to the Systematic Section alone, and 1,076 literature references dating from as early as 1717. By de Beer's own admission, it is "the outcome of some fifteen years' work devoted to the study of the development of the skull in all the vertebrate groups" (p. xxix).

The years since 1937 have seen a tremendous increase in the number of published studies that bear on aspects of vertebrate skull development of interest to de Beer. They range from clinical to evolutionary in orientation. Yet, *The Development of the Vertebrate Skull* remains a valuable reference. It still contains the most up-to-date and complete descriptions of skull ontogeny for numerous taxa. In other fields, especially developmental mechanics, its accounts have been superseded; nevertheless, it continues to provide a vital historical perspective on the evolution of ideas.

In the following pages, we highlight developments in several areas that were of especial concern to de Beer, and which remain of primary importance to questions of vertebrate structure and evolution. These center on the fundamental organization of the head; the origin and differentiation of the cells which form the skull; the nature of the primary skeletal tissues, cartilage and bone; and the evolution of skull diversity. Where possible, we have arranged these topics in the same sequence used in *The Development of the Vertebrate Skull*. By limits of space alone, we have been obliged to omit other topics equally appropriate. Readers interested in details concerning skull development in particular vertebrate groups are referred to recent reviews (e.g., Moore 1981, on mammals; Bellairs and Kamal 1981, on reptiles; other references below).

It is unlikely that anyone will ever again be able to prepare such a comprehensive and up-to-date summary of vertebrate skull development within a single volume. We can only agree with the anonymous reviewer for *Nature* (2 July 1938) who concluded: "The writing of such a book must have entailed an immense amount of careful work, and students of the morphology of vertebrates owe a debt of gratitude to the author for having carried it out so successfully."

Head Segmentation

There is perhaps no topic pertaining to the fundamental organization and structure of the vertebrate head that is more "classical" a problem than segmentation. The idea that the head is organized around a fundamental plan of serial segments dates back at least two centuries. It figured prominently in debates over vertebrate origins and relationships in the latter half of the nine-

teenth century, and this controversy carried on into the early part of the twentieth century.

De Beer considered segmentation sufficiently important to devote approximately half of his Introductory Section to it. He explicitly accepted two claims: first, following from the work of Balfour and others, that "in early stages of development the head is segmented in a manner precisely similar to the trunk" (p. 15); second, based on the observations of Marshall, that segmentation of somites arises independently of that of ventral mesoderm (i.e., visceral arches). The primary, somitic segmental pattern comprised three anterior, or prootic, somites, and a variable number of posterior, or metotic, somites (the first two metotic somites typically were transitory and contributed nothing to the adult skull). In fact, de Beer apparently considered these aspects sufficiently resolved that to him the primary remaining issues concerning segmentation were the exact number of segments incorporated into the skull in different vertebrate groups, and the causes for this variation; he reviewed the evidence accordingly. While accepting T. H. Huxley's rejection of any vertebral contribution to the skull proper (with the possible exception of the extreme posterior region), he devoted little attention to the possible segmental arrangement of cranial bones in the *adult* skull. Instead, citing the work of Severtsov, he concluded that a primitive, simple segmental pattern of dermal bones "has been obscured" (p. 33). Yet even this topic was discussed only in the context of the number of segments that contribute to the adult skull.

The certainty with which de Beer presented cranial segmentation belied both the limited state of knowledge at the time and the lack of consensus among anatomists concerning just how segmented the head really is. The picture portrayed by de Beer may have been representative of a majority view, but divergent opinions were strongly maintained in 1937 and have continued to the present day. Kingsbury (1926) and later Romer (1972) rejected the classical scheme of cranial segmentation, stressing instead the degree to which the organization of cranial tissues is fundamentally different than those behind the head. Concurrently, the Swedish school of lower vertebrate paleontology and comparative morphology (Stensiö, Holmgren, Jarvik, Bjerring) developed an extreme view in which virtually *all* cranial components may be identified with a single, unifying scheme of cranial segmentation that literally is continuous with that of the trunk (Bjerring 1977; Jarvik 1980).

These views represent radically different opinions as to the nature of cranial segmentation, yet they do share a fundamentally similar methodology: conclusions are drawn from static descriptions of relatively late-stage embryos. And it is here that research conducted in only the last few years promises to finally resolve this age-old dispute over the basic organization of the head. These studies use a vastly different methodology: detailed, electron-microscopic examination of early embryos (e.g., primitive streak, gastrula), and experimental analysis of tissue origins using permanent cell markers in chimeric grafts between related species. Two discoveries are particularly important.

The first is the unequivocal demonstration that paraxial mesoderm in the cranial region of early embryos *is* segmented. The segments, termed somitomeres, are not visible by light microscopy but are revealed clearly by the scanning electron microscope (Meier 1984). They have been observed in sal-

amanders (Jacobson and Meier 1984), snapping turtles (Meier and Packard 1984), chicks (Meier 1981), and mice (Meier and Tam 1982) and thus would seem to be a basic feature of vertebrate head organization. In the posterior region of the head, as well as the trunk, somitomeres are the precursors of somites (Jacobson and Meier 1984; Tam et al. 1982). Anterior cranial somitomeres fail to give rise to somites, but they do contribute to a number of adult tissues, namely, virtually all of the myogenic component of voluntary muscles, including the branchiomeric musculature which traditionally has been considered a derivative of unsegmented lateral plate mesoderm, or hypomere (Noden 1983*a*, *b*). In addition, there may be a fundamental difference between amniotes and anamniotes in terms of both the number of segments that contribute to the head and the number of cranial somitomeres that fail to differentiate into somites (Jacobson and Meier 1984).

The second is the demonstration that, at least in the chick, most cartilage and bone of the skull and lower jaw, and nearly all of the connective tissue of voluntary muscles, are derived not from mesoderm, whether segmented or unsegmented, but instead from cranial neural crest (Noden 1982, 1983*a*,*b*). The neural crest is initially unsegmented, but soon conforms to the segmental pattern of the somitomeres and pharyngeal pouches during migration. (For more on the neural crest, see below.)

These discoveries support parts of both the segmentalist and nonsegmentalist views described above. Yet they present an overall picture of the organization and development of the head that is radically different from any proposed earlier (Jacobson and Meier 1984; Meier 1981; Noden 1984). Resolution of several additional questions is still to come. For example, what is the relationship between segmentation of paraxial mesoderm and that of the neural tube? Neural tube segmentation with respect to the pattern of motor axon outgrowth and the distribution of sensory nerves is not intrinsic to the tube, but instead is imposed by the adjacent somites (Detwiler 1934; Keynes and Stern 1984). In the head, division of the brain anlage into segmented neuromeres comforms initially to the segmental pattern of adjacent somitomeres, but this correspondence is only transitory and is obscured during subsequent development (Meier 1982). And what is the relationship, topographically and causally, between segmentation of paraxial mesoderm and that of the visceral arches? In any event, it is clear that the revised view of head segmentation now being assembled will present an entirely new picture of the organization of the vertebrate head, including the skull.

Skull Diversity

The Systematic Section represents de Beer's attempt to amass an integrated review of all descriptive data pertaining to skull development in vertebrates. This entailed employing a standard terminology throughout, and drawing nearly all of the 143 plates for illustrated comparisons. Subsequent discussions of skull structure, homology, and evolution then were built on this base.

In the Preface, de Beer confessed the fear that his lengthy tome would have a "sterilizing" (p. xxxi) effect on the field, whereas his ultimate objective in writing the book was to provide a summary of knowledge that would facilitate

or even stimulate subsequent work on the skull. While it is not at all clear that publication of *The Development of the Vertebrate Skull* is even partly responsible, there is no denying that de Beer's fear was realized in part: skull development and structure as a discipline did not maintain the central position in considerations of vertebrate biology after 1937 that it held for preceding decades. As cited by Barrington (1973), the Additional Bibliography of the 1971 edition, which de Beer himself compiled, contains fewer than 30 papers on skull development that appeared after the book's original publication. We, however, have identified at least 125 *additional* papers published between 1937 and 1971, and 65 papers since 1971, that describe new and significant aspects of skull development in vertebrates other than standard laboratory species. Thus, whereas de Beer's Additional Bibliography is indicative of a general decline in interest in skull development after 1937, it is not an adequate representation of the studies that have been performed, including many significant contributions.

Studies of skull development published after 1937 can be considered broadly representative of three topics: vertebrate phylogeny, developmental mechanics, and evolutionary mechanisms. Each topic has been emphasized to varying degrees among the major vertebrate groups, reflecting the appropriateness of particular taxa for examining certain problems and, in some cases, their suitability for experimental manipulation.

Vertebrate Phylogeny. At the time of publication of *The Development of the Vertebrate Skull* many fundamental aspects of vertebrate relationships were unresolved. The relationships of cyclostomes to fossil jawless, as well as jawed, fishes; the closest tetrapod ancestor among lobe-finned fishes; the relationships of the three orders of modern amphibians, both among themselves and with respect to archaic taxa; and relationships among ratite birds and other flightless species are examples. Skull development is a potential source of data for establishing phylogenetic affinity and defining phylogenetic trends, but de Beer was extremely reluctant to draw phylogenetic inferences from the data he amassed; the few he offered (pp. 456–69) were intended "at least as a basis for further work" (p. xxx).

"Further work," however, has been slow in coming. The number of developmental studies applied to phylogenetic questions is slight in comparison with the number based on adult features, so that the potential use of skull development in phylogenetic analysis remains largely untapped. Nevertheless, their implications can be large. Extensive descriptions of head development in the bowfin, *Amia calva,* by the Swedish school have been used to support a radical hypothesis of polyphyletic origin of tetrapods (reviewed in Jarvik 1980). Features of cranial skeletal and circulatory development in a wide variety of Recent mammals have challenged several long-held views concerning both the reptilian-mammalian transition and the subsequent radiation of modern mammals (Presley 1979, 1981; Presley and Steel 1976, 1978). Contrasting patterns of ossification of the orbitosphenoid have been used to emphasize the phylogenetic distinction of amphisbaenid reptiles from remaining squamates, the lizards and snakes (Bellairs and Gans 1983). Yet, nearly fifty years after the publication of *The Development of the Vertebrate Skull,* many of the phylogenetic questions prominent in 1937 remain unanswered.

Two phenomena, however, may qualify the use of development in phylogenetic analysis. One is variation. Use of features of development as characters when defining phylogenetic relationships among major taxa assumes that variation at lower taxonomic levels is slight in comparison with that at higher levels. Substantial variation among closely related taxa, and certainly within species, restricts the taxonomic utility of any character. For example, development and adult morphology of the auditory bulla have been used as characters for establishing phylogenetic relationships among certain mammalian taxa. Yet, recent studies of the ontogeny of the auditory bulla reveal a diversity of developmental patterns even among genera within the same order (Novacek 1977; Presley 1978; reviewed in Moore 1981). This variation at lower taxonomic levels may limit the future use of characters of the auditory bulla in defining relationships at higher taxonomic levels (Moore 1981).

The second potential qualification is adaptation. Development itself can evolve, especially in response to selection for adaptive features. And while altered patterns of development need not affect adult features (de Beer was well aware of such embryonic or larval adaptations), they may severely restrict the use of development in phylogenetic analysis. For example, in some caecilians—limbless, viviparous amphibians which make up the order Gymnophiona—the pattern of cranial ossification is an integral component of a unique specialization for fetal maintenance via maternal oviducal secretions; it provides little information of phylogenetic value at the level of relationships among Recent or archaic amphibian orders (Wake and Hanken 1981).

Developmental Mechanics. De Beer's personal research interests and expertise lay primarily in descriptive studies (Barrington 1973). He had, however, a sincere interest and training in experimental approaches to development, as attested by two books, *An Introduction to Experimental Embryology* and *The Elements of Experimental Embryology* (the latter with J. S. Huxley). It's therefore not surprising that whereas the Systematic Section of *The Development of the Vertebrate Skull* comprises static descriptions almost exclusively, de Beer elsewhere cited the promise offered by the experimental method for revealing "causal relationships in the development of the skull," information about which was "meagre" (p. xxx).

The subsequent period has witnessed a burgeoning application of experimental approaches to elucidating the mechanics of skull development (Hoyte 1966; Moffett 1972; Dixon and Sarnat 1982). For the most part, however, these studies have been confined to only a handful of species. Thus, whereas processes of skull differentiation probably are best known for the domestic fowl (i.e., "the chick"), there have been virtually no experimental studies that have addressed skull differentiation in other birds. Extrapolation of conclusions based on only a few species to vertebrates generally is justified for certain fundamental features; developmental processes are largely conservative. Focus on a limited array of species, however, has inevitable drawbacks.

For example, hormonal mediation of epithelial-mesenchymal interactions plays a key role in the development of several nonskeletal organ systems (Cunha et al. 1983). In amphibians, initial formation of most, and in some cases all, cranial ossification centers accompanies other, widespread anatomical changes

that constitute metamorphosis from an aquatic to a terrestrial form—changes which are largely under hormonal control (White and Nicoll 1981). Yet, by focusing studies of skull development on amniotes (e.g., chick, mouse), which lack metamorphosis, researchers may have unwittingly avoided revealing a possible role of hormones in mediating epithelial-mesenchymal interactions that precede cranial osteogenesis in at least some vertebrates.

Broadening the systematic spectrum of vertebrates for laboratory experiments may also have practical benefits, as in the recent development of procedures for rearing alligator cranial explants in vitro as a model system for studying neural crest differentiation (Ferguson et al. 1983).

Evolutionary Mechanisms. Several authors recently have addressed the question of why morphology (including descriptive embryology) was, at least in the West, "excluded" from the evolutionary synthesis of the 1930s and 1940s (e.g., Churchill 1980; Coleman 1980; Ghiselin 1980; Hamburger 1980; Lauder 1982; Wake 1982). De Beer is a case in point. From E. S. Goodrich, his mentor at Oxford, he inherited a primary interest in documenting *patterns* of morphological evolution. Indeed, the Systematic Section of *The Development of the Vertebrate Skull* reflects de Beer's preoccupation, derived from nineteenth century embryology, with two themes, homology and a refutation of the biogenetic law (Churchill 1980). He, like most descriptive embryologists and morphologists at the time, was not in a position to provide the "theory of development" (Waddington 1941) that might have included morphology in the synthesis—with its emphasis on *mechanisms* of evolutionary change at the level of populations—from its earliest stages. (Lost in the lament is the fact that several outstanding descriptive embryologists and morphologists during and soon after the synthesis did continue their studies with an eye toward evolutionary mechanisms, including work on the skull. Most notable here are the Russian school of lower vertebrate morphology, particularly I. I. Schmalhausen's extensive studies of head development in salamanders of the primitive family Hynobiidae [reviewed in Schmalhausen 1968; see also Adams 1980]; and, in the United States, D. D. Davis [e.g., Davis 1964].)

One phenomenon that did receive de Beer's attention was heterochrony: variation in the timing of a developmental event. In 1930 de Beer had published *Embryology and Evolution* (later revised and issued as *Embryos and Ancestors,* 1940) in which he set forth several processes which could either advance or retard the development of a character in an individual in comparison with its ancestors and so bring about morphological change during evolution. In *Development of the Vertebrate Skull,* however, heterochrony was discussed only briefly in two contexts: the allometric relationship between facial and skull growth (pp. 471–72), and identification of the proper ontogenetic stage for making phylogenetic comparisons (pp. 447–48). In the former case, de Beer pointed to the existence of two distinct growth rates in mandibular growth—an initial rapid rate and a subsequent slower rate—the changeover often coinciding with onset of ossification. In the latter, de Beer gave some suggestion as to the mechanism of heterochronic change ("the manifestation of different rates of histogenetic activity in different regions," p. 448) and commented that evolution may make use of the effects of heterochrony ("embryonic variation may be the starting-point of variations also affecting the fully formed structure," p. 448). In

this regard he described one form of altered timing of development, namely, caenogenesis (embryonic adaptation), but had little else to say. Despite de Beer's obvious interest in heterochrony as an important mechanism of evolutionary change generally, he refrained from presenting it as more than an interesting but minor theme in skull development.

The last few years have seen a surge in the number of studies that incorporate development into analyses of mechanisms of morphological evolution. The importance of heterochronic processes was re-emphasized by Gould (1977) as acceleration or retardation of development which result in recapitulation and paedomorphosis, respectively—the earlier or later appearance of a character in a descendant than in its ancestors. Alberch et al. (1979) subsequently proposed a scheme of ontogenetic trajectories to quantify heterochrony. With this theoretical foundation, various authors have renewed the search for evidence of heterochrony and are applying such analysis to skull growth in order to relate skull ontogeny and phylogeny. Data are now available from recent studies of amphibians (Alberch and Alberch 1981; Alberch 1983; Hanken 1984; Hanken and Hall 1984; Travis 1980; Trueb 1985; Wake 1980), snakes (Haluska and Alberch 1983), birds (Grant 1981), rodents (Atchley 1983; Brylski 1985), living and fossil horses (Radinsky 1983), fossil rhinoceroses (Prothero and Sereno 1982), primates (Shea 1983), and man (Buschang et al. 1982; Gould 1977). In addition, the degree to which developmental processes may in some instances restrict variation available for natural selection, and thus constrain evolutionary change, yet in other instances facilitate the appearance of novel morphological arrangements, has been emphasized (Alberch 1982, 1983; Hanken 1983). Finally, documentation of extensive skull polymorphisms within natural populations of groups as different as cichlid fishes (Liem and Kaufman 1984), ambystomatid salamanders (Collins and Cheek 1983), and rodents (Berry and Searle 1963) further demonstrates the enormous potential for rapid and extensive morphological and ecological, and thus evolutionary, divergence conferred by heterochrony and by epigenetic developmental processes.

Despite this accumulating knowledge documenting the importance of heterochronic and allometric changes, we have only recently gained insight into the developmental processes that produce such effects. Katz (1980) related the constants of the allometric formula, $Y = bX^k$, to the relative number of cell division centers (b) and the difference between the rates of cell division (k) of two parts, Y and X; such an approach "explains" differences intrinsic in eye growth rates between the salamanders *Ambystoma tigrinum* and *A. punctatum* (= *maculatum*), documented by Twitty and Schwind (1931) more than fifty years ago. Genes are now being identified which inhibit growth of some bones while accelerating the growth of others *in the same organism* (Forsthoefel et al. 1983; Hall 1984*a*). Variation in the timing of epigenetic tissue interactions and in the initial size of skeletal blastemata have been identified as potentially important mechanisms for effecting heterochronic change (Hall 1984*b*), adding flesh to the bones of de Beer's notion of heterochrony as a "manifestation of different rates of histogenetic activity in different regions" (p. 448).

To date, however, these approaches have involved few taxa. Indeed, we still know little of the nature and extent of natural variation of skull development parameters in any vertebrate. Experimental approaches for analyzing both

developmental mechanics and developmental genetics remain underutilized in the context of skull evolution. Thus, the potential contribution of development to an understanding of the mechanisms of skull evolution remains largely untapped. The time is now ripe for new insights into heterochrony and allometry as processes guiding development and evolution of the skull.

Role of the Neural Crest

The germ layer theory was firmly entrenched at the time de Beer was writing *The Development of the Vertebrate Skull*. It held that cranial skeletal tissues (cartilage and bone) and dentine were mesodermal derivatives. Any statements to the contrary were treated as heresy. "Heretical" statements, however, were accumulating, particularly in relation to the embryological origin of the visceral cartilages. De Beer reviewed the evidence (pp. 472–76), mostly from anuran and urodele amphibians, for a neural crest (i.e., ectodermal) origin of these cartilages. Neural crest is a population of cells which break away from the neural epithelium during neurulation and assume a mesenchymal morphology as they migrate throughout the early embryo. Descriptive histology, extirpation, and grafting of neural crest cells pointed to their exclusive contribution to the visceral cartilages, but it was with evident reluctance that de Beer accepted the evidence: "It will be seen, therefore, that from the existing state of knowledge it is difficult to resist the conclusion that the cartilage of the trabeculae and visceral arches is derived from the neural crest, strange as it may seem, and great as are the difficulties presented by an attempt to frame a general theory of the origin of cartilaginous material in terms of the germ-layers" (p. 476)—not an enthusiastic embrace of a new paradigm but a grudging acceptance that a favorite theory could not accommodate new facts! (Romer [1972, p. 129] provided a similar story concerning evidence that neural crest cells contribute to the jaw cartilages in mammals, evidence "discovered in 1911, by a student working under Professor J. P. Hill of University College, London, but the fact was not published for nearly half a century [Hill and Watson, 1958]—a delay due, it seems, to reluctance of the professor supervising the student's work to commit treason to the germ layer theory!")

These and other observations soon led to rejection of a strict application of the germ layer theory (Oppenheimer 1940). In 1947 de Beer himself published a seminal paper showing that visceral arch cartilages, odontoblasts, and probably osteoblasts of dermal bone arose from neural-crest-derived (ecto)mesenchyme in *Ambystoma mexicanum*. The last sentence of the abstract reads: "The germ layer theory in its classical form must therefore be abandoned." Three years later Hörstadius (1950) published his important monograph on the neural crest.

Since then, interest in the neural crest origin of craniofacial tissues has mushroomed, both in the study of normal development and in craniofacial anomalies and neurocristopathies (tumors of neural crest derivatives). Weston's (1970) critical review stimulated much interest in migration of neural crest cells. The subsequent discovery, by Le Douarin, of a permanent marker in the form of differing patterns of heterochromatin in cells of the Japanese quail and domestic fowl opened up experimental work on higher vertebrates (reviewed in Le Doua-

rin 1982) and the prospect of accurately following cells in interspecific chimeras (Lemus et al. 1983; Noden 1982). It is now firmly established from such experimental evidence that the branchial basket of the ammocoete larva, the trabecular, visceral, hyoid, and mandibular cartilages of urodele amphibians and of larval anuran amphibians, and all of the facial and much of the cranial bone and cartilage in birds are of neural crest origin (reviewed in Hall 1980; Le Douarin 1982; Noden 1984). Control of initiation of skeletogenesis within neural-crest-derived mesenchyme, however, resides in extracellular matrices associated with adjacent epithelia (Hall 1983). Much less experimental evidence is available for the mammalian craniofacial skeleton (Hall 1980; Le Douarin 1982; Morriss and Thorogood 1978) but the evidence coming out is congruent (Erickson and Weston 1983; Flint 1983; Verwoerd and van Oostrom 1979).

It has been persuasively argued that the evolutionary appearance of the neural crest was a major event in the evolution of the vertebrate head (Gans and Northcutt 1983; Northcutt and Gans 1983). We thus today find neural crest cells finally translated from heretical outsiders knocking on the door of respectability to key members of the congregation of cells that form the vertebrate skull.

Membrane, Dermal, and Cartilage Bones

De Beer was concerned with distinguishing cartilage from bone as skeletal tissues, and membrane bones from cartilage bones as skeletal units (pp. 1–7, 495–502), the former requiring knowledge of histogenesis and ontogeny and the latter knowledge of ontogeny and phylogeny.

Russell (1916) provided a useful historical review of membrane versus cartilage bones; more recently, Delaporte (1983) surveyed the history of periosteal and endochondral ossification. We now have biochemical markers for cartilage and bone (type I and type II collagen, osteocalcin, cartilage-specific proteoglycan), so that distinguishing between the two tissues is no longer the problem it was for de Beer. Reconciliation of ontogenetic and phylogenetic data with respect to cartilage bone and membrane bone, however, remains a problem. As echoed by de Beer, joining a debate that went back to the early 1800s, "histogenesis cannot be regarded as an infallible guide to phylogeny" (p. 6). He cites T. H. Huxley's summary of both the accepted view and the resulting conundrum, namely: "It is highly probable that throughout the vertebrate series, certain bones are always, in origin, cartilage-bones, while certain others are always, in origin, membrane bones.". But what "if a membrane-bone is found in the position ordinarily occupied by a cartilage-bone, is it to be regarded merely as the analogue and not as the homologue of the latter?" (p. 4). Smith (1947) dealt with the problem simply by categorizing it, establishing separate ontogenetic and phylogenetic classifications of bone. Patterson (1977) and Reif (1982) faced it head on by following von Baer (1826) in making a fundamental distinction between the inner (endo-) and outer skeletons—the endoskeleton consisting of membrane, perichondral, and endochondral bone and cartilage, the outer skeleton of dermal bone and, in birds and mammals, secondary cartilage.

Patterson, like de Beer and Huxley before him, was particularly concerned with the question of inconvertibility of membrane and cartilage bones. All three

had made detailed studies of the head skeleton in fishes, where vertebrate skeletogenesis is at its most complex and skeletal tissues are the most difficult to classify. De Beer believed that "the membrane bones in the skin should be distinguished as dermal bones" (p. 7), and Patterson (1977) argued cogently for an absolute distinction between dermal bones and bone and cartilage of the endoskeleton. For Patterson, fusion or loss explained supposed examples of dermal bones invading the endoskeleton—an interpretation shared by Huysseune et al. (1981) in their studies of the cichlid head skeleton; by Jollie (1975) who studied *Esox;* and by Bellairs and Gans (1983) in a study of the reptilian orbitosphenoid, a membrane bone with associated cartilage nodules in the amphisbaenian, *Leposternon microcephalum,* but a cartilage bone in other reptiles. Thus, while no distinction can be made in the process of osteogenesis (ontogeny) of membrane and cartilage bones, the two ought clearly be regarded as phylogenetically separate skeletal systems. Recently, Ruibal and Shoemaker (1984) described extensive dermal bones (osteoderms) in tropical anurans, ossifications which are quite independent of the underlying endoskeleton and which appear late in postmetamorphic life. Such structures are ideal objects of further experimental study of the relationship between bone in the inner and outer skeletons.

The Relationship of Dermal Bones to Lateral Line Canals

De Beer devoted a few pages (pp. 6, 489–90, 508) and four Agenda items (**ii.**6, p. 513; **iii.**10–12, p. 514) to the problem of the relationship between dermal bones and lateral line canals. Some dermal bones (he cited nasals in flatfish; nasal, frontal, intertemporal, and postparietal in *Amia*) lie in close association with sense organs (neuromasts) of the lateral line canals, both ontogenetically and phylogentically. Is this association a causal one, with sense organs of the lateral line inducing osteogenesis, or is it only the topographical consequence of dermal bones secondarily associating with lateral line canals? De Beer saw it as secondary. He argued that many dermal bones in fishes, including several in the skull, have no association with lateral line canals, and that the homologues of canal-associated bones in fishes arise in higher vertebrates in the absence of lateral line canals. His presumption was that a causal relationship must be constant throughout all vertebrates if it is to exist in a single vertebrate group. Subsequent studies, however, show this not to be true.

For example, Meckel's cartilage is induced by embryonic epithelia in all vertebrates, but the specific epithelium which performs the induction varies from group to group: pharyngeal endoderm in amphibians, cranial ectoderm in the domestic fowl, and mandibular epithelium in the laboratory mouse (Hall 1983). Thus, the requirement for induction is constant but the specific epithelial inductor varies, and so it may be also for dermal bones in fishes. Not all dermal bones need be induced by elements of lateral line canals for some to be so induced. As noted by de Beer, "The matter could, however, be settled by the extirpation of the lateral line placode in a young embryo" (p. 489, and see Agenda, items **iii.**10–12, pp. 514–15). Only two such experimental studies are known to us.

Moy-Thomas (1941) removed the primordium of the lateral line from one side of the head of a single rainbow trout embryo prior to ossification and found that a frontal bone developed just as on the operated side. He concluded that no induction normally occurred. (He also showed that development of the frontal proceeded in embryos whose brain had been extirpated, thus ruling out any induction between brain and overlying osteogenic mesenchyme.) However, Westoll (1941) objected, arguing that dermal bones in teleosts were known to be independent of lateral line canals (e.g., regeneration of the frontal occurs independently of neuromasts [Pinganaud-Perrin 1973]), and that the experiments should be repeated using a species such as *Amia*. This challenge has been accepted only recently by Meinke (1982), who has begun studies of the role of epithelial-mesenchymal interactions in development of the dermal skeleton in fishes.

The second study is that of Devillers (1947, 1965) using *Salmo*. He found that neuromasts did act as centers of aggregation for osteogenic mesenchymal cells, the primordium of dermal canal bone. Later the cells separate from the epithelium, as does the neuromast, following which further ossification occurs around the neuromast. (A very similar series of events occurs in the development of scleral bones under epithelial scleral papillae in birds [Fyfe and Hall 1983; Murray 1943].) Devillers emphasized, as did de Beer, the dual composition of dermal canal bones: a laterosensory (tubular) and a basal (membrane) component. According to Devillers (1965), however, both components are induced by neuromasts in the salmon but only the tubular component is so induced in cyprinids. Devillers also cited unpublished work by Guinnebault showing that the parietal in the salmon, although not directly associated with a lateral line canal, "depends to some extent on the induction of the lateral line system" (1965, p. 265). The contradiction between these conclusions and those of Moy-Thomas (1941) and Westoll (1941) remains unresolved.

A different type of experimental study, by Merrilees (1975), dealt with continued deposition after skeletogenesis had been initiated. Using transplantation techniques, he showed that a specialized cord of epithelial cells in the lateral line canals of the goldfish, *Carassius auratus*, controls cavitation of the tubular component by *inhibiting* deposition of bone, cartilage, and scale. There are other skeletal systems where an epithelium initially stimulates but later inhibits skeletogenesis, as in chondrogenesis in the embryonic limb bud (Hall 1983; Solursh et al. 1984). This raises the possibility, yet uninvestigated, of initial stimulation by neuromasts and later inhibition by epithelia of the lateral line canals.

Recently, Jollie (1984*a*,*b*,*c*) provided detailed descriptions of cranial osteogenesis with respect to lateral line development in *Salmo*, *Polypterus*, and *Lepisosteus*. We know of no additional, experimental studies on origin of canal bone even though several authors have raised the neuromast-dermal bone relationship as an important problem to probe experimentally (Graham-Smith 1978; Northcutt and Gans 1983; Patterson 1977; Schaeffer 1977). Patterson (1977) also has addressed the related problem of sensory canal cartilage in elasmobranchs and its possible induction by elements of the sensory canals. What we now need are further experimental studies on elasmobranch, chon-

drostean, holostean, and teleost fishes, the fifty years since de Beer's *Development of the Vertebrate Skull* having produced only three reports for teleosts and none for remaining groups.

Secondary Cartilage

De Beer's concern with the relationship of membrane bone to cartilage bone led him to consider the significance and consequences of the presence of secondary cartilage on membrane bones (pp. 2, 38, 502, 514). Membrane and dermal bones ought not to have any association with cartilage, but scattered reports in the literature since the 1850s had pointed to nodules of cartilage on membrane bones *after* ossification had commenced (contrast with primary cartilage which *precedes* endochondral ossification), and developing quite independently of the primary cartilaginous skeleton from which it also differed histologically. Earlier, Schaffer (1930) had reviewed the known distribution of secondary cartilages which had been seen in the mandibular symphysis, on mandibular processes (condylar, coronoid, and angular), and in sutures between dermal skull bones in mammals, and on membrane bones of the craniofacial skeleton in birds. Secondary cartilage received little subsequent attention, however, until dental anatomists began to investigate the growth of mandibular processes, especially the condylar. It was then firmly established that condylar cartilage was indeed secondary and derived from periosteal cells; that it was subsequently replaced by a modified process of endochondral ossification; and that it was adaptive in origin, forming only in response to the biomechanical forces imposed by muscle action (reviewed in Beresford 1981; Durkin et al. 1973; Hall 1978; Koski 1975; Vinkka 1982). De Beer asked in his Agenda of problems for study in the future whether secondary cartilage cells could be demonstrated to turn into osteoblasts in vitro. Melcher (1971) and Silbermann et al. (1983) have demonstrated that condylar chondrocytes can.

Reinvestigation of avian secondary cartilages did not begin until the 1950s when P. D. F. Murray began a series of studies both to describe the nature and distribution of avian secondary (adventitious) cartilages (Murray 1957, 1963) and to show that mechanical forces were required to evoke them from otherwise osteogenic periosteal cells (Murray and Smiles 1965). One of us (B. K. H.) was the last of Murray's graduate students, and took up the study of avian secondary cartilage stimulated both by Murray's studies and by the Agenda set out by de Beer (reviews in Hall 1970, 1978, 1979).

Secondary cartilage is not an oddity, anomaly, or occasional aberration. It is a regular and predictable feature of both avian and mammalian membrane bones, and not just those of the craniofacial skeleton for both the avian and mammalian clavicle possess secondary cartilage (Beresford 1981; Gardner 1968). Moreover, it reflects the ability of periosteal cells to form either membrane bone or cartilage, the latter representing an adaptation to resist local mechanical stresses—at sutures and articulations, under muscle and ligament insertions (Hall 1968), or during repair of fractures (Hall and Jacobson 1975). Secondary cartilage is now beginning to take a more prominent place in basic texts (Ham and Cormack 1979) and has been the subject of a recent, authoritative, and comprehensive monograph (Beresford 1981).

But what of other vertebrates? Membrane bones (dermal in the sense of Patterson 1977) are found in all vertebrates, but secondary cartilage is restricted to birds and mammals. Cartilage in fish that superficially resembles secondary cartilage has been shown to represent nodules of primary cartilage secondarily fused to membrane bones; it also differs both histologically and histochemically from secondary cartilage (Huysseune et al. 1981; Ismail et al. 1982; Patterson 1977). Nor does secondary cartilage form during the repair of fractured membrane bones in fishes (Moss 1962). Secondary cartilage has never been described during normal development of the cranial skeleton of amphibians or reptiles (Bellairs and Kamal 1981; Hall 1984*c*), nor does it form when their membrane bones are fractured (Ferguson, personal communication; Hall and Hanken 1985), although fracture provides an environment conducive to secondary chondrogenesis in birds and mammals (Jolly 1961; Hall and Jacobson 1975). Development of the ability of periosteal cells of membrane bones to form secondary cartilage thus appears to have been a late event in vertebrate evolution (Hall 1984*c*; Hall and Hanken 1985). More experimental studies on fish, amphibian, and reptilian membrane bones would greatly aid in identifying how the skeletogenic potential of their periostea evolved.

Cartilage in the Cyclostomes

Skeletal tissues of agnathans always have been central to debates concerning the origin of vertebrates from non-vertebrate chordates, and concerning the relationships among jawless and jawed fishes. This has never been more true than the last few years, during which time several authors have evaluated the dramatic possibility of a close phylogenetic relationship between lampreys and gnathostomes, distinct from hagfish (Jensen 1963; Schaeffer and Thomson 1980; Hanken and Hall 1983; Løvtrup 1984; Mallatt 1984). Major differences in the published descriptions of the skeletal tissues in the two modern-day agnathan lineages are consistent with this idea of their phylogenetic independence.

De Beer briefly discussed a peculiar skeletal (connective?) tissue found in the head of the ammocoetes (lamprey) larva and known as mucocartilage (pp. 38–39, 41–46). It has a basophilic extracellular matrix like cartilage, and is rich in elastic fibers like elastic cartilage. Yet, it is restricted to the larval stage and was variously regarded as being either transformed into or replaced by the "true" cartilage of the adult. For de Beer, mucocartilage "does not deserve the name of cartilage at all . . . [and is] nothing but a particular kind of connective tissue" (p. 45).

Wright and Youson (1982) recently reexamined mucocartilage in *Petromyzon marinus* and described a surrounding, vascularized "perichondrium" rich in collagen and elastic-like microfibrils. The enclosed mucocartilage is avascular, lacks collagen, is sparsely cellular, and, like the investing membrane, contains elastic-like microfibrils. They side with de Beer and with Hardisty (1979) in regarding mucocartilage as a specialized larval connective tissue. Its developmental fate, however, remains uncertain and requires further detailed study, for adult cartilage apparently may develop where no mucocartilage existed, within degenerating mucocartilage, or even within degenerating larval muscle.

Wright and her colleagues also have investigated the structure and biochem-

istry of adult cartilage, in both the lamprey, *Petromyzon marinus* (Wright and Youson 1983; Wright et al. 1983), and the hagfish, *Myxine glutinosa* (Wright et al. 1984). Lamprey cartilage is highly cellular with a central zone of hypertrophic chondrocytes. It is bounded by a vascular perichondrium which contains collagen fibrils, and has an extracellular matrix which consists of a dense network of branched, non-collagenous fibrils composed of the protein, lamprin. Lamprin, which comprises approximately one-half of the dry weight of the annular cartilage (glycosaminoglycans, the normal major constituent of cartilage, make up less than 5 percent of the dry weight of lamprey cartilage), has only traces of hydroxyproline, no hydroxylysine, and much tyrosine and histidine. The hagfish has two different types of cartilage, one with branched fibrils of a protein similar to lamprin, termed myxinin, the other with hypertrophic cells filled with cytoplasmic filaments and very similar to some of the invertebrate cartilages (Wright et al. 1984).

We see encapsulated here the difficulty and inconsistency in the classification of these skeletal tissues. Mucocartilage is bounded by a perichondrium but is not considered cartilage because it lacks collagen. In the adult tissue the matrix also lacks collagen and has minimal glycosaminoglycans, but it is regarded as cartilage! (A similar difficulty arises with the invertebrate cartilages, many of which lack type II—"cartilage-type"—collagen; see Person [1983] for a very useful discussion on how to define cartilage.)

Notwithstanding these questions concerning appropriate terminology, published descriptions of the skeletal tissues of lampreys and hagfish are consistent with the idea of an early separation and long, independent evolution of the two groups. We urge caution, however, as many differences may just reflect the stages studied. Very recently, Robert Langille, working in the laboratory of B. K. Hall, has shown considerable similarity in the ultrastructural organization of cartilage of spawning adult lamprey and the type I hagfish cartilage published by Wright et al. (1984). Such similarity, seen at only certain phases of the life cycle, may further complicate the use of developmental data in the interpretation of the exact relationships among cyclostomes and gnathostomes.

This brings us full circle to the use of developmental studies to understand phylogeny, a major aim of de Beer's fifty years ago, and a coupling that once again has brought the skull into center stage.

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