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BRAIN HETEROCHRONY AND ORIGIN OF THE MAMMALIAN MIDDLE EAR

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The mammalian middle ear forms a distinctive chain of tiny ossicles whose parallel histories in ontogeny and phylogeny are among the most famous in comparative biology. During pre-mammalian history the auditory chain was attached to the mandible, where it functioned in sound transmission to the inner ear. In mammals ancestrally the chain was torn free from the mandible and displaced to a new position behind the jaw. In early mammalian ontogeny the auditory chain begins development as a part of the mandible that is later torn free and displaced backward, recapitulating the evolutionary transformation. Participation by mandibular elements in auditory transmission predates the origin of mammals by more than 100 million years; what is distinctly mammalian is that the mandibular elements become detached from the jaw and repositioned behind it. Two competing theories have attempted to account for this transformation. An evolutionary hypothesis argues that natural selection for improved high frequency audition is the mechanism, while a developmental hypothesis contends that ontogenetic onset of functionality in jaw muscles is the driving mechanism. Neither hypothesis accounts for both the evolutionary and developmental transformations, or for the repositioning of the ossicles behind the jaw.

Phylogenetic analysis indicates that the distinctive inflated mammalian neocortex arose at the same time that the middle ear became detached from the jaw, in the last common ancestor of extant mammals. A study of cranial development in didelphid marsupials using high resolution X-ray CT, histological, and cleared and stained specimens implicates differential growth of the brain in detachment and repositioning of the ossicles. In early ontogeny the brain is a hydrostat that mechanically loads and displaces surrounding tissues, and in mammals it grows to unprecedented size. The ear ossicles approach their mature size during the third week of postnatal development while still attached to the jaw and participating in a continuous arcade of elements extending from the fenestra vestibuli to the mandibular symphysis. The brain continues to grow for nine additional weeks and in the process it bursts the arcade. As the circumference of the growing brain expands, the ossicular chain is torn away from the mandible and carried backwards to its adult position behind the jaw. Unlike the competing hypotheses, the geometry of the growing brain accounts for detachment of the auditory chain from the mandible in both ontogeny and phylogeny, for the precise path of subsequent posterior displacement of the auditory chain during development, and for the timing and extent of this movement. A heterochronic increase in the rate and duration of brain development, which arose in Mammalia ancestrally, may have been the driving force behind the origin of the distinctive middle ear.

Introduction

The study of evolutionary morphology is more than a century old, yet one might argue that we remain largely ignorant of the mechanisms of morphological change that have operated historically. While many potential mechanisms have been identified and some studied experimentally, very few are yet mapped onto phylogenies and hence few historic instances of transformation are fully explained. This situation promises to improve with the emergence of the new discipline of evolutionary developmental biology (Hall, 1992; Hanken, 1993; Hanken and Hall, 1993; Wake et al., 1993, 1996), and as it becomes more fully integrated with phylogenetic systematics. The recognition of heterochrony requires an explicit, corroborated phylogenetic framework and it is this point that makes phylogenetic systematics fundamental to understanding the evolution of development (Fink, 1982; Kluge, 1988). Together, phylogenetic systematics and evolutionary developmental biology afford means to recognize episodes of heterochrony and heterochronic cascades, to discriminate between genetic and epigenetic factors controlling development, and to map onto cladograms these hierarchical agents of change as they have operated historically.

An illustration of how these disciplines might be integrated can be found in a problem involving the origin of the mammalian middle ear (Rowe, 1996), in what is among the most famous transformations in comparative anatomy. The middle ear in extant mammals forms a chain of ossicles that hangs suspended from beneath the adult cranium and comprises one of the most distinctive osteological characters of mammals. The parallel ontogeny and phylogeny of these bones is one of the most celebrated recapitulations known (Goodrich, 1930; de Beer, 1958). The middle ear bones began their phylogenetic histories as hearing ossicles while located in an ancient position extending between the fenestra vestibuli, their point of connection to the inner ear, and the dentary bone of the lower jaw. The ear ossicles thus participated in a continuous arcade of elements extending from the mandibular symphysis to the cochlear housing of the skull. The craniomandibular joint was formed between two bones in the chain, the quadrate and articular, which served the dual functions of hearing and feeding (Allin, 1975, 1986; Bramble, 1978; Crompton and Parker, 1978; Kemp, 1982; Kermack and Kermack, 1984). Over a 100 million year span of pre-mammalian history the middle ear ossicles were gradually reduced in size while the dentary was enlarged until it came to participate in the craniomandibular joint. In the next step of this history, coinciding with the origin of the "crown group" Mammalia, hearing and feeding were decoupled as the chain of ossicles became detached from the mandible. The dentary bone was the only element remaining in the lower jaw, and the craniomandibular joint was established

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solely between the dentary and squamosal bones. During this transformation, the morphology of the ear ossicles and their anatomical relationships to one another were largely conserved, but as a group they migrated to a new location entirely behind the condyle of the dentary. Detachment of the ossicles from the mandible produced the condition that occurs universally among adult mammals and that, under the typological practices of Linnean taxonomy, was widely regarded as the definitive mammalian character (Olson, 1959; Simpson, 1959). Despite its importance, the mechanism causing this evolutionary detachment of the auditory ossicles from the jaw and their backward displacement has remained poorly understood.

In the early ontogeny of extant mammals several of the middle ear bones differentiate and begin to grow in their primitive positions along the mandible and, for a time in early development, there is a continuous chain of cartilages extending from the oval window to the mandibular symphysis. Later, the ossicular chain separates from the mandibular arch and moves backwards from the jaw to assume its derived position suspended solely by the cranium in a new location entirely behind the mandible. Ontogeny thus recapitulates phylogeny in what would seem to be a highly unlikely transformation, the detachment of the ossicular chain from the mandible and its repositioning in a new location behind the jaw (Toeplitz, 1920; de Beer, 1937, 1958; Rowe, 1988; Filan, 1991).

The evolutionary transformation from a "mandibular ear" (suspended between cranium and dentary) to a "cranial ear" (suspended only from the cranium) involved significant redesign of the most intricate regions of the skull. If the ear functioned for 100 million years while attached to the mandible, why did it detach and shift to a new location? Why is this transformation recapitulated in the ontogeny of extant mammals? My goal in this study is to describe the morphogenesis of detachment and repositioning of the chain of middle ear ossicles in ontogeny and phylogeny. Although generally viewed as the culmination of a long, gradual evolutionary history, I argue later that the episode of detachment occurring in the last common ancestor of extant mammals was qualitatively different from the preceding 100 million year history of ossicular reduction.

Two hypotheses, one evolutionary and one developmental, have attempted to account for the detachment of the ossicles. The evolutionary hypothesis (Allin, 1975) views pre-mammalian history as being shaped by selection for high frequency hearing. It views the detachment of the ossicular chain from the mandible as merely an extension of this trend, but it says nothing of the developmental mechanism that might have engineered this transformation. The developmental hypothesis (Herring, 1993a; Maier, 1987), on the other hand, argues that the onset of functionality of the jaw muscles tears the chain away from the mandibular arch but it does not attempt to describe this transformation in an evolutionary framework. Neither hypothesis addresses both the developmental and phylogenetic transformations, however, nor do they explain the repositioning of the auditory chain to its new location behind the craniomandibular joint. Are the evolutionary and developmental hypotheses complementary, or are they mutually exclusive? Does some other single mechanism address both the ontogenetic and phylogenetic transformations?

Answers to these questions may lie not so much in the ear and craniomandibular joint, where they are usually sought, as in the developmental and phylogenetic history of adjacent parts, particularly the brain. The histories of the mammalian middle ear and brain were believed to be largely independent of each other and to be the evolutionary products of separate morphogenetic mechanisms, an image compounded in the paleontological literature by assertions of convergent evolution in both regions. But unrecognized associations between the brain and middle ear emerge by mapping the variable features of both regions onto a corroborated phylogeny of mammals and their closest extinct relatives (Figs. 1, 2). These associations manifest the hierarchy of heterochrony and implicate a single cascading mechanism in both the ontogenetic and phylogenetic transformations of the mammalian middle ear.

Materials

This study of ontogeny and phylogeny was based upon osteological preparations of adult and developmental specimens of a diversity of mammalian species, and examination of the major collections of synapsid fossils in North America, Europe, Russia, and South Africa. The principal source of developmental information was a densely sampled growth series for the extant didelphid marsupial *Monodelphis domestica*. Didelphids are among the least-encephalized of living mammals and most closely resemble the ancestral mammalian condition in many features pertinent to the present study (Jerison, 1973; Reig et al., 1987). A growth series of more than 200 individuals was obtained from the Southwest Research Foundation (San Antonio, Texas). In *Mono-delphis domestica*, the gestation period is 14–15 days (Fadem et al., 1982; Kraus and Fadem, 1987). The life span of *Monodelphis domestica* is approximately 3 to 4 years. The term "adult" in this case refers to "retired breeders" that were shipped without precise age data by Southwest Research Foundation but with the general description that retired breeders range in age from 9 to 36 months. Specimens dating from postnatal days 0, 1, 10, 15, 27, and 36 were serially sectioned using conventional histological techniques and stained with azocarmine. Approximately 100 specimens dating from day 0 through adults were cleared and double stained for cartilage and bone, and dried skeletons dating from postnatal day 27 through adults were also prepared.

Serially sectioned embryos of *Didelphis* documenting the earliest stages of skeletal condensation (stages 32–35 of McCrady, 1938) were generously provided by the Wistar Institute. These specimens comprise a small fraction of the extensive collection described in McCrady's (1938) classic monograph on embryology of the opossum. Most of this once preeminent collection was tragically lost in the 1950s, but a few sets of serial sections survived and were sent to me by Wistar. I located some additional fragments of the collection

in the National Museum of Medicine. The stains are now badly faded on nearly all surviving slides, but the preparations are still useful for studying the early phases of skeletogenesis; catalog numbers indicate that they include several of the sets of sections used by McCrady to define the developmental stages of *Didelphis*.

To augment conventional developmental preparations, complete three-dimensional data sets of dried *Monodelphis* skulls dating from day 27 through old age were generated using an ultra high resolution industrial X-ray CT scanner (Rowe et al., 1993; 1995). This tool can exceed the resolution of medical CT scanners by two orders of magnitude and it produced exceptional imagery of complete *Monodelphis* crania in 100 μ thick consecutive serial sections. A complete 3-D data set of imagery was generated for each of 5 skulls along sagittal, coronal, and transverse axes. A comparative framework for studying the CT imagery of *Monodelphis* was provided by an earlier study (Rowe, et al., 1993, 1995) in which a 3-D data set of CT imagery for the extinct synapsid *Thrinaxodon liorhinus* was generated in 200 μ consecutive serial sections along the three orthogonal axes. *Thrinaxodon* (Figs. 1, 2) has long been of central interest in early mammalian history because it preserves much of the primitive morphology that we might expect to have been present in a distant ancestor of mammals. The opportunity to compare serial sections of individual specimens simultaneously along different axes while handling the intact specimens themselves offered an exceptionally rich opportunity to visualize all details of complex three-dimensional morphology in comparing the derived *Monodelphis* with its more primitive relative *Thrinaxodon*. The *Thrinaxodon* specimen was generously made available by the Museum of Paleontology, University of California, Berkeley (sp. no. UCMP 40466).

Systematic Framework

The systematic framework of this analysis was critical to its outcome. The following discussion is based on the understanding that mammals are the sister group of other extant amniotes (Fig. 1), a conclusion that rests upon analysis of developmental and adult morphology of both hard and soft tissues in a series of phylogenetic tests that included both extinct and extant taxa (Gauthier et al., 1988, 1989; Gauthier, 1994). The term Mammalia is a node-based name (de Queiroz and Gauthier, 1990, 1992, 1994) for a clade whose membership derives from ancestry rather than "defining" characters. The name is used in reference to the taxon stemming from the last common ancestor of extant mammalian species (Rowe, 1988, 1993; Rowe and Gauthier, 1992), what is sometimes referred to as the "crown group" Mammalia.

Two additional taxa are referred to below that include mammals and some of their extinct relatives (Figs. 1, 2). The term Cynodontia is another node-based name referring to the taxon stemming from the last common ancestor shared by Mammalia and the extinct Late Permian taxon *Procynosuchus* (Kemp, 1979, 1980; Rowe, 1993). Cynodonts thus include mammals and their closest extinct outgroups. The extinct taxon *Thrinaxodon* is a basal member of Cynodontia whose anatomy is almost uniformly plesiomorphic. *Thrinaxodon* has been of interest to paleontologists for more than a century in understanding the 100 million years of history immediately prior to the origin of mammals (Rowe, 1993; Rowe, et. al., 1993, 1995). The term Synapsida refers to a still more inclusive taxon (Fig. 1). Synapsida is a stem-based name (de Queiroz and Gauthier, 1990, 1992, 1994) for the taxon that includes mammals and all extinct taxa closer to mammals than to other extant tetrapods (Gauthier et al., 1988; Rowe, 1988).

The phylogeny of mammals and their extinct relatives has received a great deal of attention over the last century and it was one of the first segments of Vertebrata to be studied phylogenetically (McKenna, 1975). During the last decade, a number of independent analyses of early mammalian phylogeny were conducted (Gauthier et al., 1988; Rowe, 1988, 1993; Wible, 1991; Wible and Hopson, 1993) using taxon/morphological-character matrices designed for analysis with maximum parsimony software such as PAUP (Swofford, 1986–1994), MacClade (Maddison and Maddison, 1992), and HENNIG 86 (Farris, 1986). Although these studies reached different conclusions on certain points of relationship among extinct taxa, the results for all extant and most extinct taxa were identical. The studies also disagreed in certain judgments on character independence that caused different authors to split or lump suites of cranial features along different lines. This disagreement is significant from systematic and morphological standpoints, but the conflicting decisions on how to score characters did not affect the topology of the most parsimonious trees generated in the separate studies. In fact, in two batteries of tests (Rowe, 1988, 1993), characters of the skull could be entirely removed from the data matrix and the postcranial data alone recovered the same tree as did the complete skeletal data set for the taxa of interest to the present study. The trees in Figures 1 and 2 show only points of relationship that are consistent with all analyses, and they provide the systematic context in which the histories of the middle ear and brain are discussed below. Readers are referred to the original analyses for details of phylogenetic methodology.

Paleontologists have long maintained that both the mammalian middle ear (Olson, 1959; Simpson, 1959; Kermack and Kermack, 1984; Allin, 1986; Miao, 1991) and inflated brain (Kielan-Jaworowska, 1986; Miao, 1991) evolved convergently among synapsids. The genealogy supporting this view was developed with phenetic methods which treated Mammalia as an evolutionary grade and held that participation by the dentary and squamosal bones in the craniomandibular joint constituted achievement of that grade (Rowe, 1993). Under the phenetic paradigm, the Late Triassic-Early Jurassic fossils *Morganucodon* and *Sinoconodon* were viewed as the oldest mammals because they are the oldest fossils that have a load-bearing dentary-squamosal joint, and their anatomy was taken to reflect the ancestral states of mammalian characters. Because they retain a mandibular ear and an uninflated brain, it followed that the ancestral mammal did as well (Patterson and Olson, 1961; Edinger, 1964; Hopson, 1979; Crompton and Jenkins, 1973; Jerison,

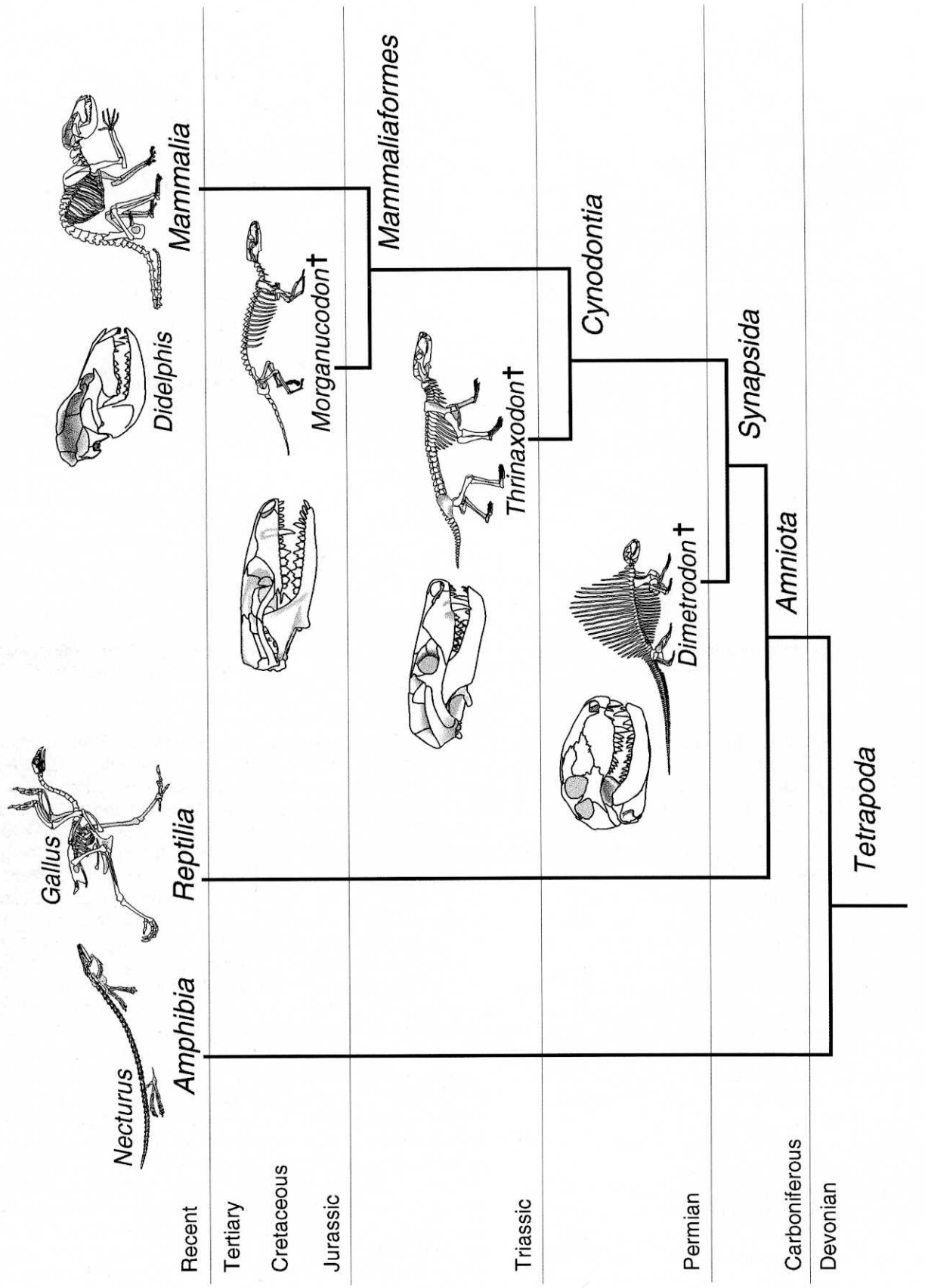

FIGURE 1. Phylogeny of the major groups of extant tetrapods and selected extinct relatives of mammals, based on phylogenetic analyses by Gauthier et al. (1988) and Rowe (1988, 1993).

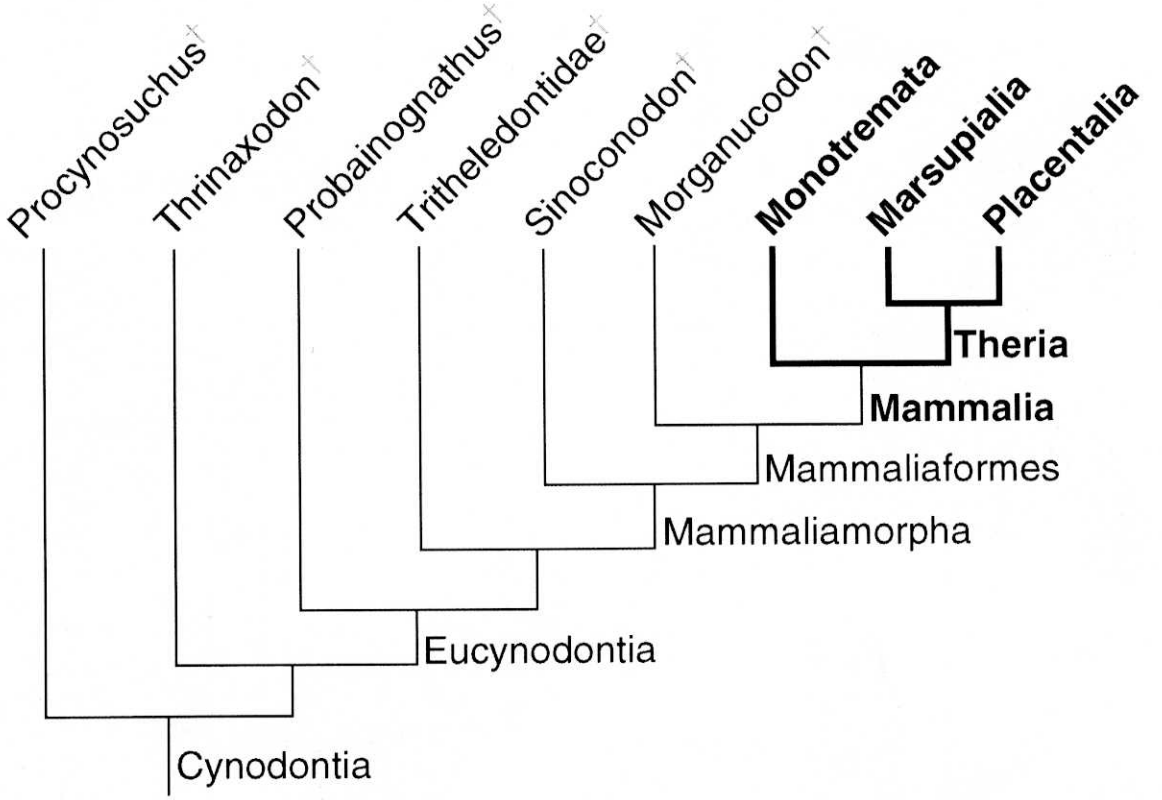

FIGURE 2. Phylogeny of the major groups of living mammals and some of their closest extinct relatives among Cynodontia. The topology among these taxa is consistent with the results of separate analyses by Kemp (1983), Gauthier et al. (1988), Rowe (1988, 1993), Wible (1991), and Wible and Hopson (1993).

1973, 1990). Consequently, the inflated brain and "cranial" ear must have evolved convergently in the lineages containing modern monotremes and therians after the two groups diverged from their last common ancestor.

In contrast, the more recent phylogenetic outlook views Mammalia as a clade, a position corroborated by the many features from all systems that distinguish mammals from other extant taxa (e.g., appendix B in Gauthier, et al., 1988). Additionally, there are extensive lists of synapomorphies from all parts of the skeleton based on analyses of extant species and fossils (Gauthier et al., 1988, 1989; Rowe, 1988, 1993; Wible, 1991; Wible and Hopson, 1993; see also Kemp, 1983, Zeller, 1993). The analyses concur that monotremes and therians are more closely related to each other than to *Morganucodon* or *Sinoconodon*, and that the latter two taxa are consecutive plesiomorphic outgroups to Mammalia (Figs. 1, 2).

Phylogeny of the Middle Ear Ossicles

Early in synapsid history, the bones adjacent to the craniomandibular joint (CMJ) undertook the new function of transmitting airborne sound vibrations to the inner ear while maintaining their primitive structural role in the masticatory system (Allin, 1975, 1986; Crompton and Parker, 1978; Gauthier et al., 1988, 1989; Kemp, 1982; Kermack and Kermack, 1984). An unbroken chain of bones extended from the fenestra vestibuli to the symphysis of the mandibles and at first "mandibular" hearing was probably restricted to low frequencies owing to the massiveness of all bones in the transmission pathway. Vibrations received by the mandible reached the inner ear via the articular and quadrate, which formed the CMJ, and from the quadrate via a massive stapes to the fenestra vestibuli (Fig. 3). A rich fossil record documents the gradual increase in relative size of the main tooth-bearing element, the dentary bone, while the "post-dentary" elements, the articular, prearticular, surangular and angular, were reduced to tiny, delicate ossicles. The quadrate, quadratojugal and stapes, which were suspended from the cranium throughout this history, were also reduced. Over roughly 100 million years of pre-mammalian history, the bones of the auditory chain were gradually reduced while the dentary took on a correspondingly increased structural role in the mandible.

Biomechanical analyses describe the reduction of the bones in the auditory chain as a sound transduction mechanism increasingly sensitive to high frequencies (Allin, 1975, 1986; Bramble, 1978; Crompton and Parker, 1978; Kemp, 1982; Kermack and Kermack, 1984). A host of intricate oropharyngeal functions unique to mammals probably arose concurrently (Smith, 1992; Crompton and Hylander, 1986). *Morganucodon* is a transitional form in that its middle ear ossicles morphologically resemble and probably functioned much like

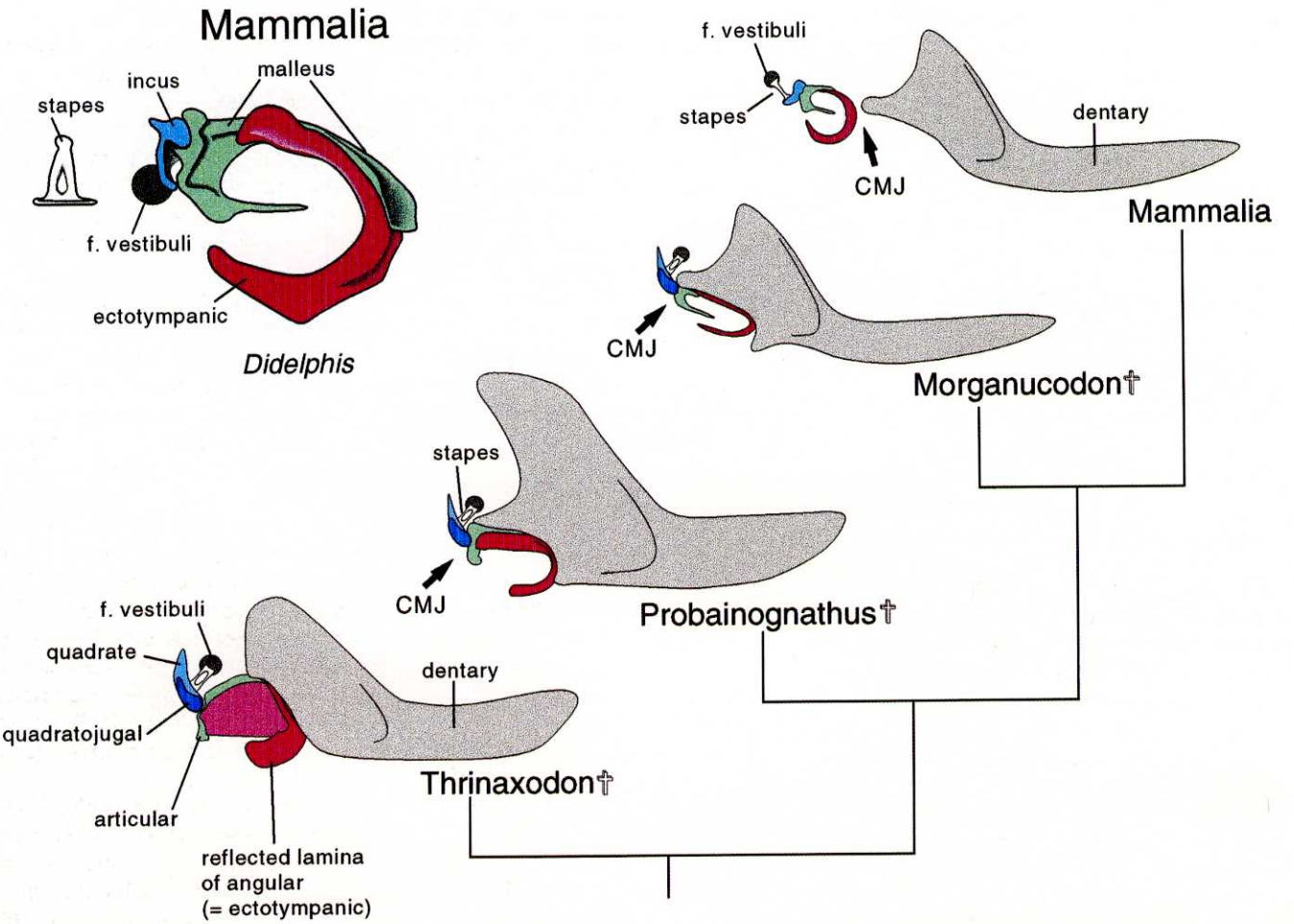

FIGURE 3. Major stages in the evolution of the mammalian mandibular arch. The angular (= ectotympanic) is shaded red, the articular (= malleus) is in green, the quadrate (= incus) is in light blue and the quadratojugal is in dark blue (after Rowe, 1996).

the mammalian ossicles (Allin, 1975), but they remained attached to the mandible where they articulated into a narrow groove along the medial edge of the condylar process of the dentary and hung suspended beneath the dentary. The quadrate and articular also persisted as structural elements in the CMJ (Crompton and Hylander, 1986). In pre-mammalian synapsids, mastication and hearing were never fully decoupled.

This situation is transformed in mammals, in which the postdentary bones are separated from the mandible in adults. In addition, the entire auditory chain is displaced to a new position entirely behind the mandibular condyle where it is suspended solely by the adult cranium (Fig. 3). The dentary alone forms the adult mandible, and together the dentary and squamosal form the entire CMJ (Kemp, 1983; Gauthier et al., 1988, 1989; Rowe, 1988, 1993; Wible, 1991). The origin of mammals coincided with the shift from a mandibular ear to a cranial ear as the auditory and masticatory systems became decoupled. In many mammals the ear ossicles are widely separated from the new CMJ and lie behind intervening secondary auditory structures such as a tympanic recess or bulla, which are derived features within Mammalia (Rowe, 1988, 1993). In their new position, the quadrate (= incus) remains attached proximally to the stapes and distally to the articular (= malleus), while the prearticular (= os goniale) and surangular (= ossiculum accessorium mallei) are tightly bound or fused to the articular, and the articular is ligamentously attached to the angular (= ectotympanic or tympanic) which supports the tympanum. The pre-mammalian linkages between the postdentary elements of the auditory chain are thus largely conserved. The major difference is that the quadratojugal fails to ossify and is represented, if present at all, by a thin ligament. Apart from becoming separated from the dentary and repositioned behind it, the mammalian cranial ear probably functions much as did the mandibular ear of *Morganucodon* (Allin, 1975, 1986).

Biomechanical models elegantly explain the pre-mammalian evolutionary reduction of the ear ossicles as a function of hearing and integrated compensatory change in the mandible (Allin, 1975, 1986; Bramble, 1978; Crompton and Parker, 1978). But these models fail to predict or

even explain detachment and repositioning of the auditory chain, admitting that the function of the auditory chain was probably not significantly altered by its detachment from the mandible. Some other mechanism must be involved.

Associated Characters

The phylogenetic analysis of mammals and their extinct relatives provided a suite of additional synapomorphies that diagnose Mammalia and that arose at the same time the auditory chain was displaced from the dentary. The association is complex, involving the reduction and loss of bones that were present in *Morganucodon* and more distant out-groups, as well as fusions between elements that primitively remained separate throughout life. Hypertrophy and heterotopy occurred in other elements, and structures that presumably were primitively cartilaginous later became ossified. Nevertheless, their phylogenetic association raises the possibility that some or all of the transformations occurring in Mammalia ancestrally shared a common morphogenetic origin.

In the skull, the pterygoid transverse process and paroccipital process were both reduced in size. The quadratojugal and tabular were lost, as were the proatlas, atlantal rib, and axial prezygapophysis in the neck. The squamosal became hypertrophied to form the entire roof of the glenoid fossa. Also hypertrophied are the occipital condyles, which became extended upwards to enclose roughly two-thirds of the foramen magnum. The distal end of Reichert's cartilage became fused to the otic capsule where it ossifies to form the adult mammalian styloid process. Other fusions occurred between the atlantal intercentrum and neural arches to form the distinctive ring-like mammalian atlas. Between these modifications of the atlas and those of the occipital condyles, the mammalian craniovertebral joint was substantially redesigned. The cribriform plate was ossified, and the maxillary turbinates became ossified as well. In addition, secondary ossifications appeared on the limbs and girdles. More detailed discussions of these and other characters are presented elsewhere (Rowe, 1988, 1993; Gauthier et al., 1988; Wible, 1991).

While there is no obvious pattern linking all of these structures, a large number of them cluster around the brain and lie in the same degree of proximity to the brain as the middle ear ossicles. The influence of an inflated brain was suggested earlier as a dominant morphogenetic influence in shaping the unique features of the mammalian skull (Rowe, 1988, 1993). The nature of this influence can be seen more clearly by comparing the pattern of skeletal change with a common pattern found in the development and phylogeny of the brain.

Ontogeny and Phylogeny of the Mammalian Brain

A large brain of unique design is one of the most characteristic features of extant mammals (Fig. 4). The central region of the forebrain, the telencephalic pallium, differentiates in a singular pattern to form the isocortex (neocortex) and pyriform cortex (Northcutt, 1984; Ulinski, 1986; Reiner, 1991; Butler, 1994). The mature isocortex forms two inflated hemispherical lobes linked by a well-developed dorsal commisure. Each hemisphere has a columnar organization of six radial layers that are generated in ontogeny by waves of migrating cells which originate from the ventricular zone and move radially outwards (Rakic, 1974, 1988; Walsh and Cepko, 1992) and tangentially (Tan and Breen, 1993) to achieve their adult positions. This inside-out pattern of neural development is unique to mammals (Butler, 1994) and is responsible for much of their comparatively huge cortical volume. The mammalian cerebellum is also large in comparison to that of other vertebrates, with an extensively infolded surface and a distinct central lobe or vermis (Edinger, 1964; Jerison, 1973; Gauthier et al., 1988). For convenience, I refer to these features collectively as an "inflated" brain. The cerebellum follows a different developmental pattern than does the cortex, but the cortex and cerebellum share a common history in that an episode of expansion in both regions occurred simultaneously with the detachment of the ossicular chain.

The fossil record of extinct synapsids reveals several successive episodes of cerebral inflation (Fig. 5). During early synapsid history, the primitive tetrapod condition obtained in which the brain failed to fill the adult endocranial cavity. There is evidence in the orbitosphenoid bone of basal synapsids and basal therapsids that the olfactory bulb was suspended at the rostral end of a long thin peduncle which transmitted the olfactory tract (Romer, 1940; Cluver, 1971). Apart from this, few details of brain structure are preserved (Jerison, 1973; Hopson, 1979; Ulinski, 1986).

The basal cynodonts *Procynosuchus* (Kemp, 1979, 1980) and *Thrinaxodon* (Hopson, 1979; Rowe et al., 1993), from the Late Permian and Early Triassic, respectively, are the first synapsids in which the brain filled the adult endocranial cavity. Information about the external morphology of the brain is preserved in these taxa in the form of natural endocasts and in the impressions left by the brain on the inner surfaces of the bones that enclose it. The data sets generated using X-ray tomography (Rowe et al., 1993, 1995) were especially informative in interpreting bone morphology with respect to the structure of the brain (Figs. 6–8). The olfactory bulbs appear as a slight swelling at the rostral end of the forebrain. This reflects a second step toward the mammalian condition in that the olfactory tracts have evidently become engulfed from behind by the cortex, so that the olfactory peduncle and external expression of the olfactory tract are absent, as in mammals. At this stage, however, the circular sulcus, which topographically demarcates the olfactory bulb and cortex in mammalian brains (Figs. 4, 5), is not yet reflected in either endocasts or the bones that lie adjacent to these structures. The forebrain was narrow, undivided, and tubular with broad dorsal midbrain exposure between the cerebrum and cerebellum. A long, narrow pineal foramen (Fig. 6D) indicates the persistence of a pineal eye. Comparison of the cross-sectional anatomy of *Thrinaxodon* and *Monodelphis* in coronal (Fig. 6) and transverse (horizontal) CT imagery (Fig. 7) provides a graphic view of the extent to which the brain expanded during the subsequent descent of mammals.

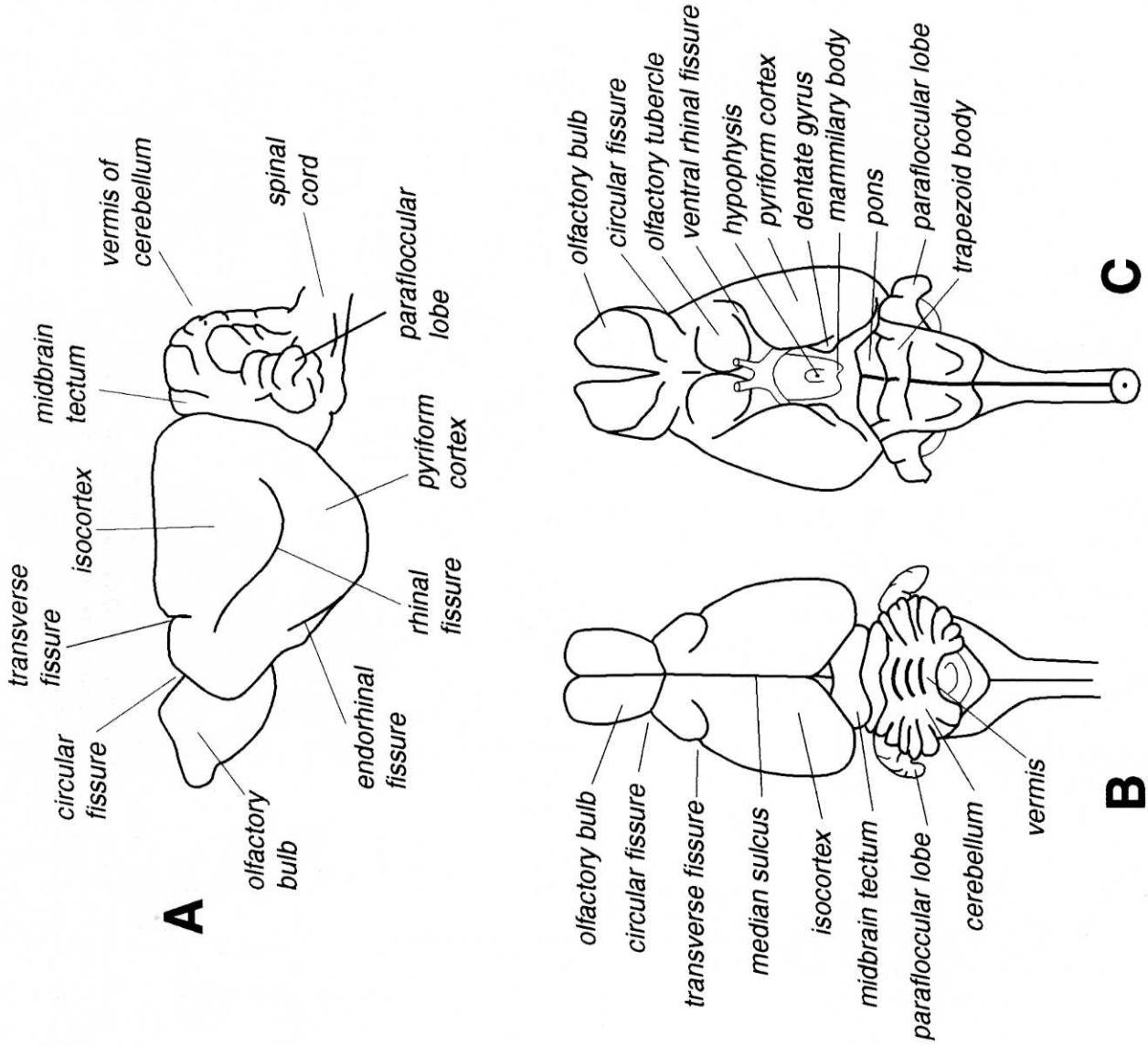

FIGURE 4. Diagram of the brain of *Didelphis virginiana* in left lateral (A), dorsal (B), and ventral (C) views. Based on Ulinski (1971) and Wyman (in Coues, 1872).

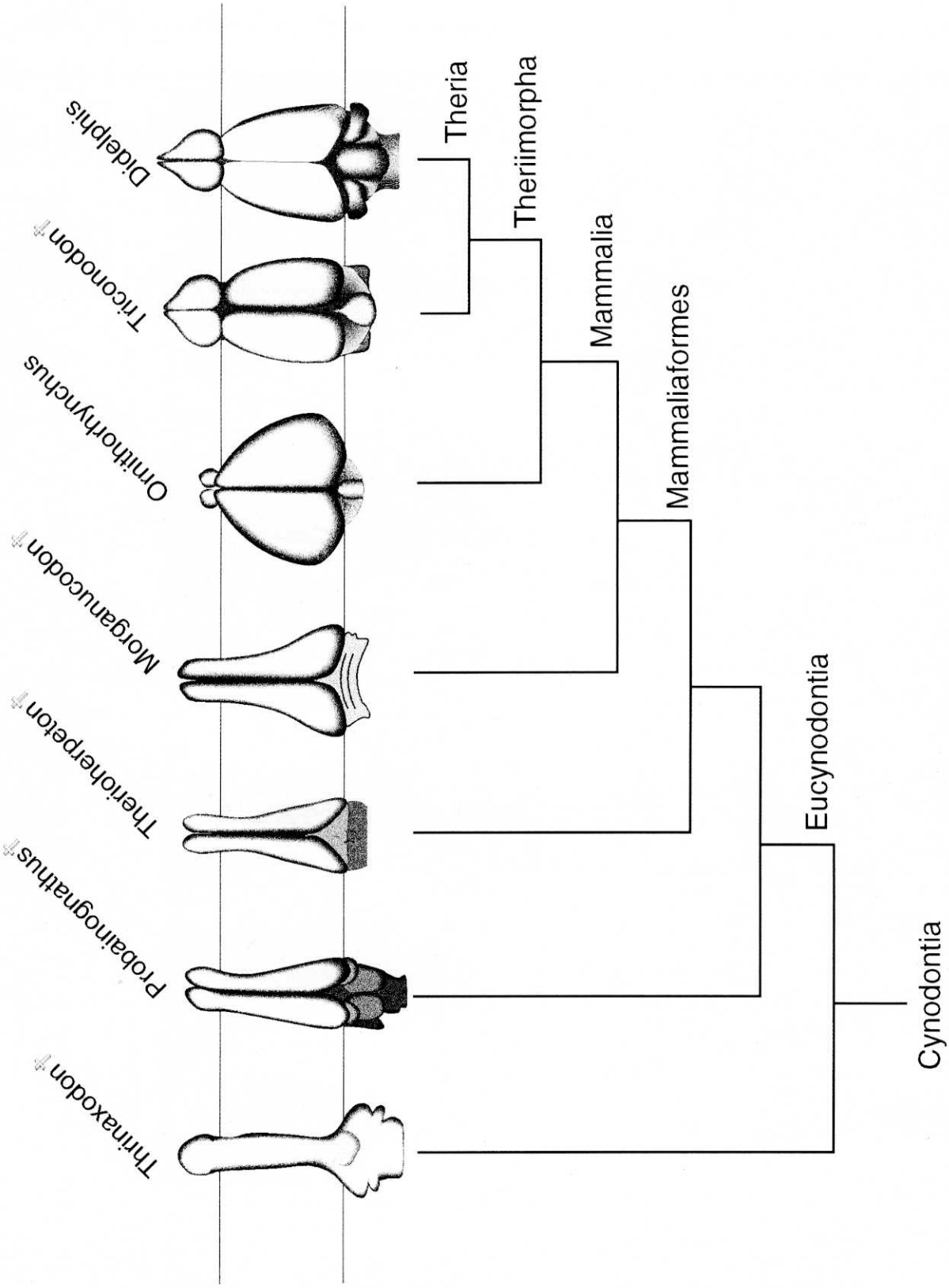

FIGURE 5. Cynodont endocasts in dorsal view, mapped onto a phylogeny of cynodonts (from Rowe, in review). *Thrinaxodon* is based on endocasts illustrated by Hopson (1979) and high resolution X-ray CT imagery of *Thrinaxodon* (Rowe et al., 1993); *Probainognathus* endocast is after Quiroga (1980); *Therioherpeton* endocast is after Quiroga (1984); *Morganucodon* endocast illustrated from impressions on fronto-parietal bones (Kermack et. al, 1981); *Triconodon* endocast is after Simpson (1927); *Ornithorhynchus* and *Didelphis* were illustrated directly from latex endocasts made from Recent specimens.

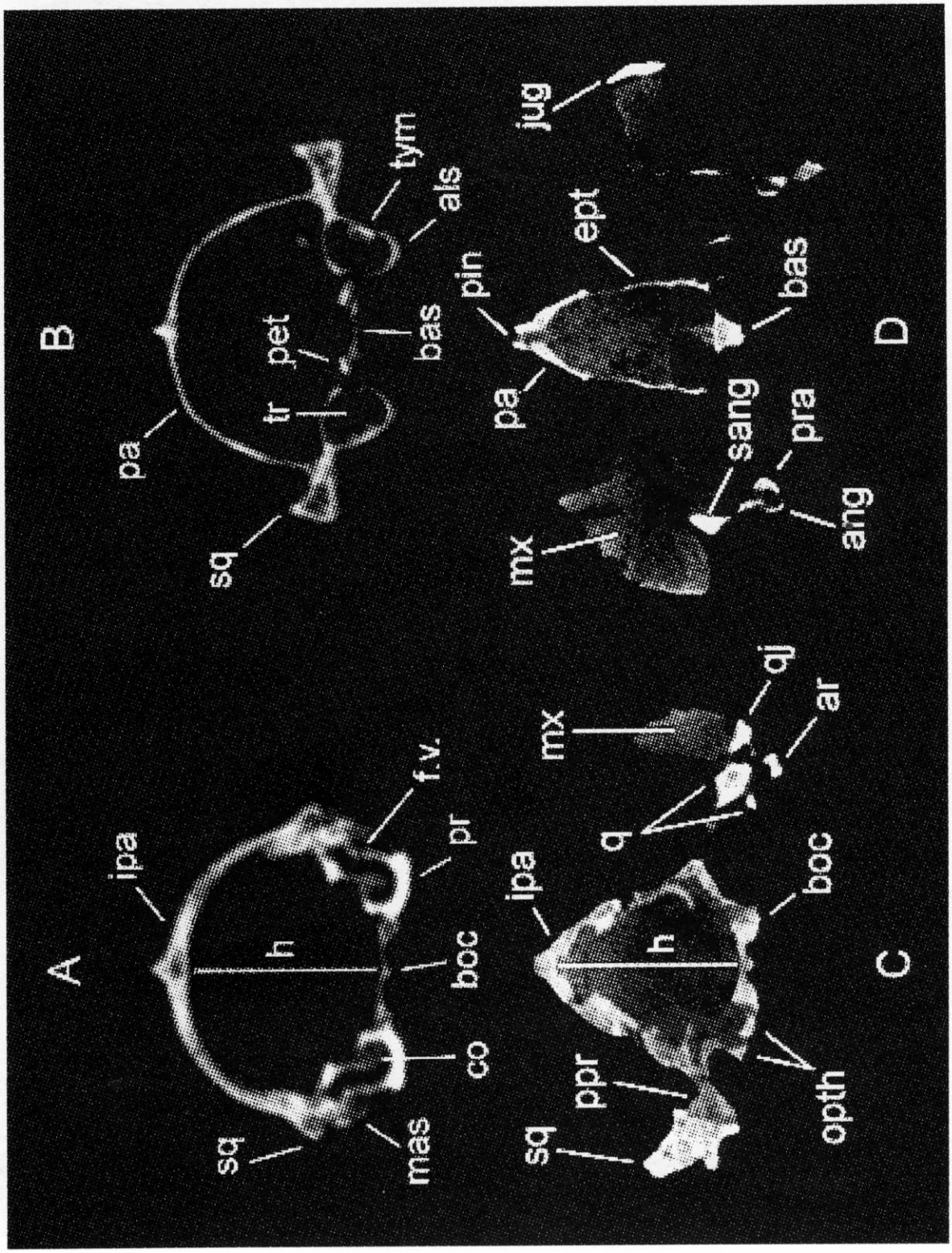

FIGURE 6. Coronal X-ray CT sections through comparable regions in *Monodelphis domestica* (A, B) and *Thrinaxodon liorhinus* (C, D), scaled to the same endocranial height (h). Sections A and C transect the cochlear region. Sections B and D transect the skull further forward, near the level of the hypophysis. A and B are from Rowe (in press); C and D are from Rowe et al. (1993). See List of Abbreviations for key.

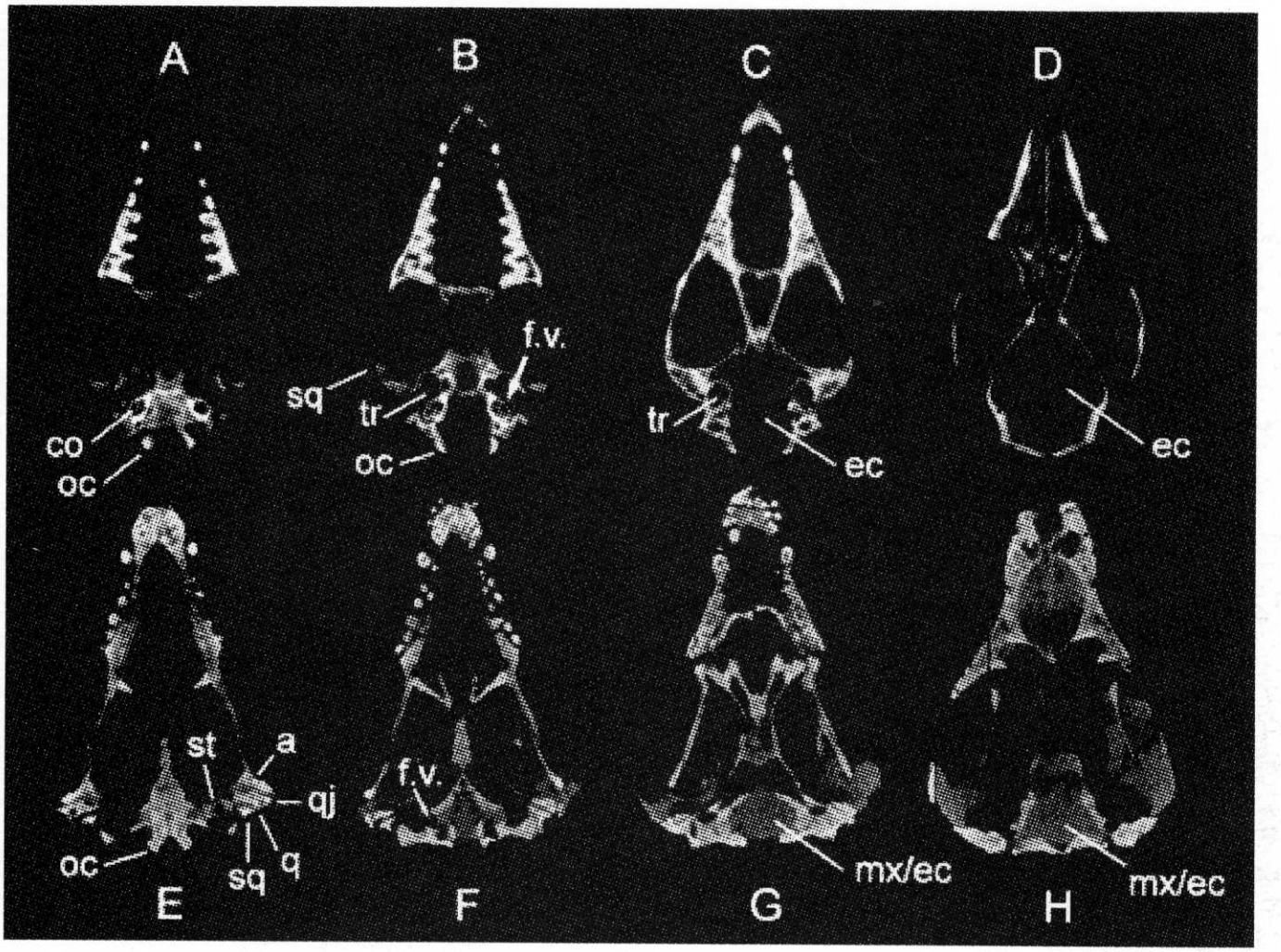

FIGURE 7. Transverse X-ray CT sections through *Monodelphis domestica* (A-D) and *Thrinaxodon liorhinus* (E-H). Sections A and E transect the floor of the braincase; sections B and F transect the fenestra vestibuli; sections C and G transect the middle of the foramen magnum; and sections D and H transect the roof of the foramen magnum. From Rowe (1996). See List of Abbreviations for key.

A second episode of cerebral inflation is recorded in an endocast of the Middle Triassic cynodont *Probainognathus* (Quiroga, 1980). The endocast of *Probainognathus* is for the first time "brain-like" (Jerison, 1973) and has begun to leave deep impressions of its outer surface in the walls of the osteocranium. There is now a median sulcus marking the division between right and left olfactory bulbs and dividing the forebrain into two incipient cerebral hemispheres (Fig. 5). At this stage the "hemispheres" remain more tubular than hemispheric, but cortical volume is relatively larger than in *Thrinaxodon*. The pineal foramen is closed and the pineal eye lost. The midbrain remains exposed dorsally, but it is sunken between the enlarged forebrain and cerebellum.

A somewhat more inflated brain is reported in the taxon stemming from the last common ancestor of mammals and tritheledontids, on the basis of fossils from Early Jurassic sediments (Rowe, 1993). *Therioherpeton* (Quiroga, 1984), a poorly known basal member of this group (Fig. 5), has a brain-like endocast reportedly larger than *Probainognathus* (Quiroga, 1980) but no newly differentiated features are discernible. Scaling may introduce an element of artifact into the perception of a larger brain, for the basal members of this clade are much smaller than *Probainognathus* and more distant cynodonts. Other early Jurassic fossils indicate that further inflation occurred in the taxon stemming from the last common ancestor of *Sinoconodon* and mammals. This is suggested by such features as bulging of the parietals outward into the temporal fenestra and bony flooring beneath the cavum epipterycum (Crompton and Luo, 1993; Rowe 1993). The inner surfaces of the parietal-interparietal of *Sinoconodon* (Patterson and Olson, 1961; Edinger, 1964; Jerison, 1973) and *Morganucodon* (Kermack et al., 1981) preserve impressions left by the divergent caudal poles of the forebrain, which span a wider curvature than in *Therioherpeton*. Like those of more plesiomorphic cynodonts, however, the olfactory bulbs remained almost cylindrical and lacked any topographic demarcation from the cerebrum. Additional plesiomorphic features include confinement of the

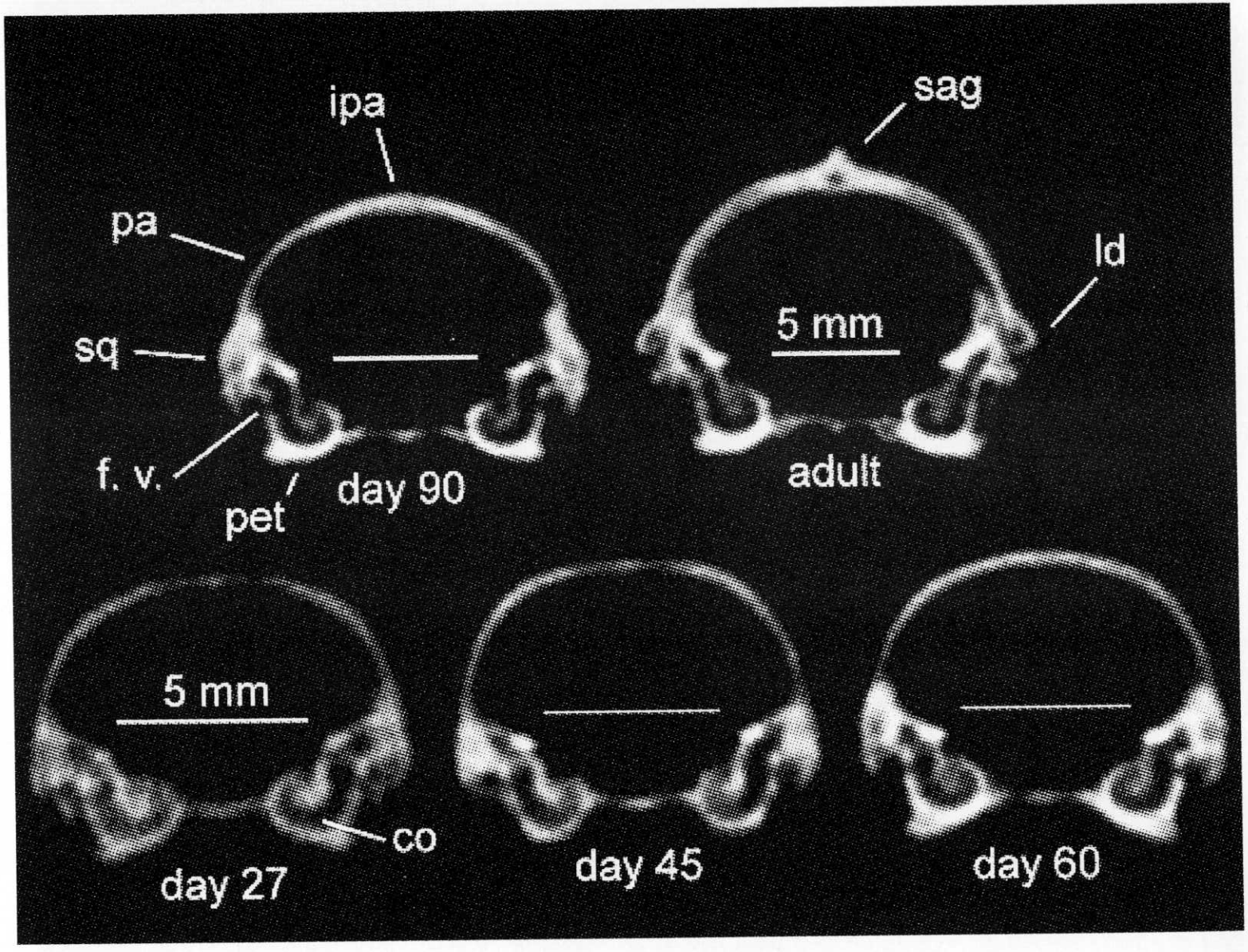

FIGURE 8. Coronal X-ray CT sections through a growth series of skulls of *Monodelphis domestica*, scaled to the same size (from Rowe, in press). All sections represent 100 μ thicknesses and transect the fenestra vestibuli (f.v.), where the stapes passes sound vibrations to the middle ear. The scale bar is 5mm in all sections. Note the progressive thickening of the parietal (pa) and interparietal (ipa) bones and the formation in the adult of the sagittal (sag) and lambdoidal (ld) crests. See List of Abbreviations for key.

cerebral hemispheres to a narrow space between the ascending processes of the epipterygoids (alisphenoids), persistent exposure of the midbrain dorsally, and the front of the braincase remaining unenclosed.

The next major episode of cerebral expansion is recorded in features shared by all extant mammals and which are most parsimoniously interpreted as having arisen in their last common ancestor. The olfactory bulbs are inflated, hemispherical, and sharply differentiated in their external morphology from the cortex by the circular fissure, which now is visible on endocasts for the first time (Fig. 5). The forebrain is greatly inflated into two hemispherical lobes that expand backwards to cover the midbrain. It appears that this is the point in history at which the cortex differentiated into a separate isocortex and pyriform cortex. The isocortex, present in all mammals, is recognizable in endocasts of relatively primitive mammals by its degree of inflation, convex hemispherical form, and backward expansion over the midbrain. In external morphology of the brain itself, the isocortex is also distinguished by both the circular fissure and rhinal fissure. The rhinal fissure classically has been used to identify the isocortex boundaries in endocasts of placentals (Jerison, 1973, 1990). However, it is rarely discernible in endocasts of the small, primitive taxa of relevance here. For example, the rhinal fissure is visible on the surface of didelphid brains (Ulinski, 1971) but it does not appear in their endocasts. The circular fissure is generally discernible in small endocasts and is the more diagnostic of the two fissures among the taxa of interest. An additional innovation of the mammalian brain is that the cerebellum is inflated and deeply folded, with a distinct vermis projecting rostrally along the midline between the caudal ends of the cerebral hemispheres. These cerebellar features are not discernible in the bones of the braincase of *Morganucodon* and more distant relatives.

The oldest fossils preserving skeletal apomorphies derived within Mammalia are from Middle Jurassic sediments (Rowe, 1988, 1993), and an endocast displaying the mammalian features described above is preserved in the Late Jurassic *Triconodon mordax* (Simpson, 1927). In *Triconodon* the mandible is comprised solely of the dentary, and its enclosed Meckelian sulcus indicates that the ossicular chain had become detached from the jaw. The preserved features in this endocast are similar to didelphid endocasts in shape and relative size (Fig. 5). In later mammalian history the rate of brain evolution varied remarkably among the lineages that have survived until today, with didelphids reflecting the least subsequent evolution and cetaceans and primates showing the greatest. Cerebral inflation in mammals is widely held to have evolved in relation to the invasion of a nocturnal and perhaps arboreal niche. Cortical expansion and differentiation into isocortex and pyriform cortex support heightened olfactory and auditory senses (Jerison, 1973), and coincident, overlapping sensory and motor maps of the entire body surface (Lende, 1963a, b, c). Cortical expansion has also been implicated in the evolution of endothermy (Jerison, 1973; Allman, 1990). The enlarged cerebellum is related to the adaptive coordination of movement through a complex three-dimensional environment (Thach et al., 1992).

The origin of the inflated brain in mammals reflects an episode of heterochrony in which the brain began to grow both faster and longer into ontogeny than it did in non-mammalian cynodonts. This is clearly an instance of peramorphosis, where the descendant ontogeny transcends the terminal state achieved during development by its ancestors (Gould, 1977; Alberch et al., 1979; Fink, 1982; Kluge, 1988). Without more knowledge about the relative timings and growth rates of developmental trajectories in the extinct outgroups, it is not possible to discern what type of peramorphosis (hypermorphosis, acceleration, predisplacement) has occurred. In the absence of direct experimental evidence, the most likely genetic moderation of this event now appears to lie in the homeobox genes and homeodomain proteins which direct early patterning in vertebrates generally (Rakic, 1988; Wilkinson et al., 1989; Keynes and Lumsden, 1990; Gilbert, 1991; Langille and Hall, 1993; Rubenstein et al., 1994; Holland, 1996:63–70). In the developing hindbrain, homeobox genes control the identity of rhombomeres, which are segmental bulges that confine clones of cells and domains of differential gene expression (Walsh and Cepko, 1992). Forebrain segmental patterning is now known to be under a similar control (Rubenstein et al., 1994). Simply specifying more segments during early pattern formation may produce an enlarged adult brain, although there is as yet no experimental verification (Marx, 1992). Whatever the genetic control, it is evident that a heterochronic perturbation of the central nervous system occurred in mammals ancestrally, producing differential growth of the brain that launched a cascade of secondary, epigenetic effects.

Epigenetic Influences on Cranial Development

It is well established that familiar physical forces and dynamic processes are significant mechanisms in pattern formation and morphogenesis throughout ontogeny (Oster et al., 1985, 1988; Newman and Comper, 1990). These forces and processes include, among others, gravity (Malacinski, 1984), adhesion (McClay and Ettensohn, 1987; Armstrong, 1989), diffusion (Crick, 1970), interfacial tension (Steinberg, 1978; Heintzelman et al., 1978), mechanical loading (Hoyte, 1966, 1975; Moss, 1968; Hall, 1984a,b,c, 1992; Wong and Carter, 1990; Herring, 1993a,b), electrical potentials (Bassett, 1972; Metcalf and Borgens, 1994; Metcalf et al., 1994), maternal biological rhythms (Lloyd and Rossi, 1993), viscous flow, phase separation, Marangoni effects, convective fingering, chemical concentrations, and density (Newman and Comper, 1990). Newman and Comper (1990) argued that morphogenic and patterning effects are the inevitable outcome of these recognized physical properties of cells and tissues. Many of these forces and processes can affect skeletogenesis, and there is ample observation and experimentation to indicate that the skeleton is responsive to a hierarchy of such influences from the time of earliest condensation of proskeletal tissues through old age (Wong and Carter, 1990).

Newman and Comper (1990) refer to these mechanisms as "generic" physical processes, while others (e.g., Hall, 1990, 1992; Herring, 1993a,b) refer to them under the more

inclusive term "epigenesis." These forces may complement and act in concert with biomolecular (genetic) processes, or they may operate by themselves, or not at all in any particular developmental episode. When invoked, they may have broad spatial effects that touch different populations of cells and different tissue types. Many of these processes are known to have nonlinear responses to relevant control variables, such that small changes in rate or magnitude of a process, or through limited interaction between parts can lead to profound effects in the resulting morphology (Mittenthal, 1989). Hall (1990, 1992) refers to this as the spatial and temporal cascading effect of ontogeny, which can produce new and unexpected consequences for adult structure. Major morphological reorganizations in phylogenetic lineages may arise by the action of these mechanisms at different times in ontogeny. The effects potentially are more profound as the forces act during earlier stages in development.

A vast medical, anatomical, experimental, and theoretical literature describes the response of postnatal craniofacial growth in humans and other placental mammals to mechanical loading (e.g., D'Arcy Thompson, 1942; Huber, 1957; Moss, 1958, 1968; Hoyte, 1966 1971, 1975; Bassett, 1972; Pritchard, 1972; van Limborgh, 1972; Buckland-Wright, 1978; Spyropoulos, 1978: Babler and Persing, 1982; Hurov, 1986; Storey and Feik, 1986; Carter, 1987; Carter and Wong, 1988; Wong and Carter, 1990; Herring, 1993a,b). In the earliest stages of skeletal development, mechanical loading is probably far less important to basic patterning than cell-to-cell adhesion, surface tensions, chemical gradients, and other epigenetic forces that act primarily at molecular and cellular levels. But from the time that tissues are differentiated and individual organs begin to grow, a new level in the epigenetic hierarchy may be expressed as loads are generated by differential growth.

Growth and form of the skull reflect the dynamic interaction of structural elements and epigenetic forces throughout ontogeny. Through much of organogenesis and early growth, the most significant forces are generated by expansion of the brain and its special sense organs, especially the eye. That the embryonic brain actually loads surrounding tissues is evident in the nature of its growth. Brain enlargement in early ontogeny is driven by a combination of tissue growth and hydrostatic volume increase in the medullary cavity. Following neurulation, the tubular brain becomes a hydrostatic reservoir as the rostral neuropore closes and the spinal neurocoel becomes occluded and the medullary cavity between them fills with an increasing volume fluid. Proper intraventricular pressure is required to drive brain expansion (Jelinek and Pexieder, 1968; 1970a, b; Desmond and Jacobson, 1977; Goodrum and Jacobson, 1981; Pacheco et al., 1986). The law of LaPlace describes the distending tension in the wall of a cylindrical vessel at any given pressure as directly proportional to the vessel's radius (Gardner, 1973; Pacheco et al., 1986). The volume of the medullary cavity increases at a linear rate while brain tissue growth increases exponentially, in part as a mechanical requirement to prevent the brain from bursting as its outer tension rises. Cerebral loading onto surrounding tissues is thus proportionate to the sum of hydrostatic load plus the load from the growing cerebral tissue. Severe deformities of the skull accompany pathologies such as microcephaly and anacephaly, which result from disruptions in ventricular pressure during early development (D'Abundo, 1905; Weed, 1920; Nañagas, 1925; Young, 1959; Hoyte, 1966; Moss, 1968; Gardner, 1973; Herring, 1993a).

By the time the first skeletal condensations appear in mammals, the tissues in which they differentiate are already stretched around a cylinder that is relatively larger than that occurring even in the terminal stages of ontogeny of the closest extinct relatives of mammals. As can be seen in the comparative CT sections of *Monodelphis* and *Thrinaxodon* (Figs. 6, 7), the mammalian bones span cerebral surfaces of greater curvature and are correspondingly thinned, suggesting that the materials to construct the skull did not increase at the same accelerated rate of growth as the brain. In *Monodelphis* the cranium is largely enclosed by bone in the fourth week but the brain continues to grow through the twelfth week and the skeleton is continually remodeled throughout the intervening period (Fig. 8). Both experimental and teratological evidence indicate that cerebral loading affects skeletal growth from the very beginnings of mesenchymal condensation, through chondrogenesis, and for a considerable portion of skeletal growth.

In addition to influencing connective tissue growth, mechanical loads can direct cell differentiation. An outstanding example is the adaptive and compensatory responsiveness of mammalian secondary cartilage and intramembranous bone to loading in the mechanical environment created during the repair of bone fractures, an ability that is expressed early in ontogeny and which persists into adult life. For example, along angulated fractures in broken limb bones, first chondrogenesis and then endochondral ossification are induced by compressive loads on the concave side, while intramembranous ossification commences on the convex side of a repairing shaft (Pritchard, 1972; Hall, 1975, 1984a, b, c, 1992; Herring, 1993b; Wong and Carter, 1990). Another such modulation is the condylar secondary cartilage of the mammalian dentary. Loading initiates the differentiation of secondary cartilage in cells that can differentiate either as chondroblasts or osteoblasts. Reduction of condylar loading suppresses secondary chondrogenesis and initiates intramembranous ossification (Hall, 1984a, 1992; Herring, 1993b).

The developing cranial muscles may generate loads of comparable magnitude to those of the developing brain as they grow and begin to twitch and contract, and they have been implicated in the detachment of the auditory chain (Herring, 1993a; Maier, 1987). Experimental data indicate that embryonic muscular movement not only loads the skeleton, but that these loads are critical to the proper differentiation of joints and joint capsules (Drachman and Sokoloff, 1966; Murray and Drachman, 1969; Laing, 1982). As muscles approach maturity they become capable of exerting far greater levels of load than the growing brain or developing myoblastemata. Muscular loading induces the mature form of such features as the coronoid and angular processes of the mandible, it contributes significantly to shaping the ma-

ture craniomandibular and craniovertebral joints, and to growth of the lambdoidal and sagittal crests (e.g., Hoyte, 1966, 1971, 1975; Spyropolous, 1978; Hurov, 1986; Carter, 1987; Carter and Wong, 1988). In generating these extreme levels of force, muscular loading can induce a new level in the hierarchy of epigenesis which may be expressed long into ontogeny after the effects of differential growth are spent (Fig. 8).

When Maier (1987) and Herring (1993a) implicated muscle loading in the detachment of the auditory chain, they followed earlier authors (e.g., Allin, 1975; Crompton and Parker, 1978) in supposing that mammalian ontogeny recapitulates the transformation between two functional joints, that is from a functional primary CMJ between the palatoquadrate and articular cartilages to the mature CMJ between the dentary and squamosal bones. More recent research suggests that this is not the case. In a histological study of the developing CMJ in *Monodelphis*, Filan (1991) found no evidence to suggest a functional joint ever forms between the quadrate and articular cartilages before they become detached and the dentary-squamosal joint becomes functional. In captivity, the young do not begin eating solid food until they are 4 to 5 weeks old (Fadem et al., 1982; Kraus and Fadem, 1987), following detachment. Secondary condylar cartilage and the beginnings of a synovial capsule also appear during the fourth week at the joint between the dentary and squamosal and signal the onset of CMJ loading by the masticatory muscles that insert on the dentary. It is difficult to precisely define a time at which the dentary-squamosal joint becomes functional, because for a time the contacts between condylar cartilage and the squamosal and the auditory ossicles and the otic capsule are equally large (Clark and Smith, 1993). As ontogeny progresses, the masticatory muscles transmit increasing loads to the CMJ and correspondingly its surface increases, mostly through a process of lateral accretion as the width between the right and left CMJs increases (Fig. 12).

Muscular loading fails to completely explain the developmental transformation of the ear ossicles in mammals. While muscular loading might contribute to early differentiation of the mandibular and auditory elements and to the initial tearing of the connective tissues that bind the ossicular chain to the mandible, this interpretation is complicated by the timing of the event in different mammals. In marsupials it takes place after birth and the young have begun to suckle, while in placentals it occurs before birth, making it difficult to identify a common mechanical setting. More importantly, the force trajectories of the masticatory muscles are oriented in such a way that the mandibular condyle is pulled upwards and backwards into the roof of the glenoid, compressively loading the craniomandibular joint (Crompton and Hylander, 1986). It is difficult to see how this action could lead to the posterior repositioning of the auditory chain behind the dentary condyle; masticatory loading would be more likely to press the dentary backwards against the postdentary bones than to separate the two. If the masticatory musculature is involved at all, its role is only part of the story and some other mechanism must be responsible for widely separating the auditory chain from the mandible.

Development of the Middle Ear Ossicles

The developing auditory chain has both endochondral and intramembranous components, and both types have attachments to the mandible that are broken as ontogeny progresses. Three cartilages are present at birth in *Monodelphis*. The stapes has already budded from Reichert's cartilage and forms a tiny rod with a small footplate that lies in the center of the opening of the fenestra vestibuli. Both the stapes and the petrosal eventually contribute to the formation of the mature footplate in later in ontogeny as a complex stapedial articulation develops at the fenestra vestibuli. Articulating with the distal end of the stapes is the caudal moiety of the palatoquadrate cartilage, which is braced against the ventrolateral edge of the otic capsule and which will ossify to form the incus (= quadrate). Meckel's cartilage forms a continuous elongate rod that bends downward at its rear end at nearly a right angle (Fig. 9). During the second week, the rear extremity is cleaved from the mandibular ramus of Meckel's cartilage, forming the cartilage in which the malleus (= articular) ossifies. The two pieces become separated when Meckel's cartilage degenerates and is resorbed during ossification of the dentary.

The intramembranous ossifications have a contrasting developmental history. At birth, both the dentary and ectotympanic (= angular) have begun to ossify in a common membranous sheet external to Meckel's cartilage, but at this stage their growth centers are widely separated and an expanse of connective tissue intervenes (Fig. 9). During the first three postnatal weeks, the ectotympanic grows in positive allometry relative to the dentary. As the ectotympanic grows, it expands against the developing angular and condylar processes of the dentary, and the two bones are held together by fibrous connective tissue that arises in the osteogenic membrane. During early ontogeny the ectotympanic lies in its ancestral position hanging beneath the condylar process of the dentary. By the end of the third week the ectotympanic is approaching its adult size. At this time its growth rate slows and shifts into a negative allometry that persists for the remainder of ontogeny. At roughly this same time, the ectotympanic is torn free from the dentary (McClain, 1939; Clark and Smith, 1993). During the next 9 weeks the auditory chain migrates backwards from beneath the condylar process and eventually comes to rest entirely behind and medial to craniomandibular joint (Figs. 3, 9).

The key to understanding both the detachment and subsequent relocation of the auditory chain may lie in an interplay between the differential growth among elements of the mandibular arcade and the brain. The brain balloons upwards and backwards from the developing facial skeleton and grows steadily for the first 12 weeks (Fig. 10) of postnatal ontogeny (Ulinski, 1971). The relative positions of the CMJ and fenestra vestibuli are convenient markers to follow in tracing cranial remodeling in the wake of cerebral growth (Figs. 11,

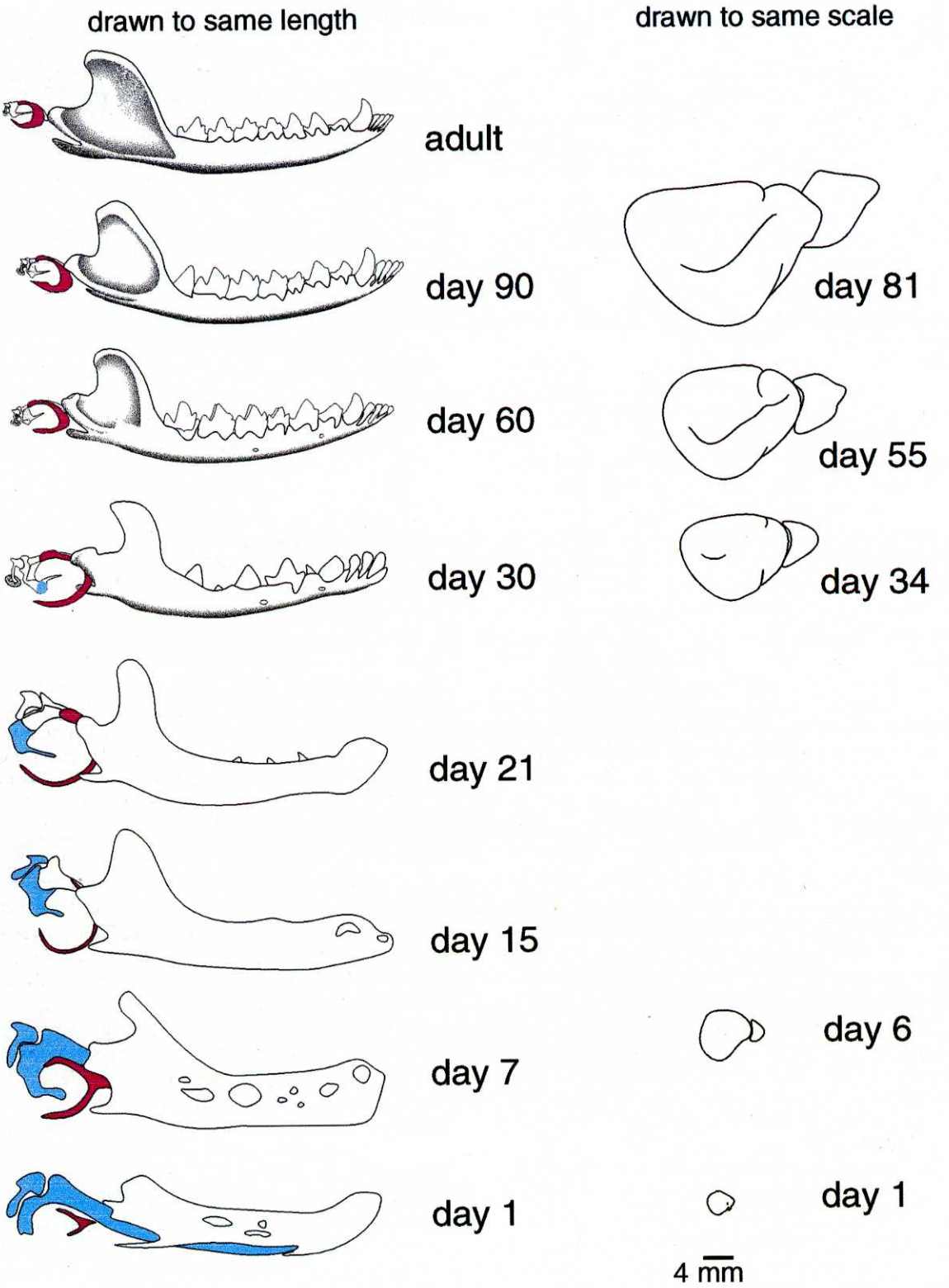

FIGURE 9. Left: Development of the mandibular arch in *Monodelphis domestica*, based on video imagery of a cleared and double-stained growth series, drawn to same length. Cartilage is shaded blue and the membranous ectotympanic is in red. Right: Growth of the forebrain in *Didelphis*, from birth to adult (modified after Ulinski, 1971), drawn to same scale. Based on Rowe (1996).

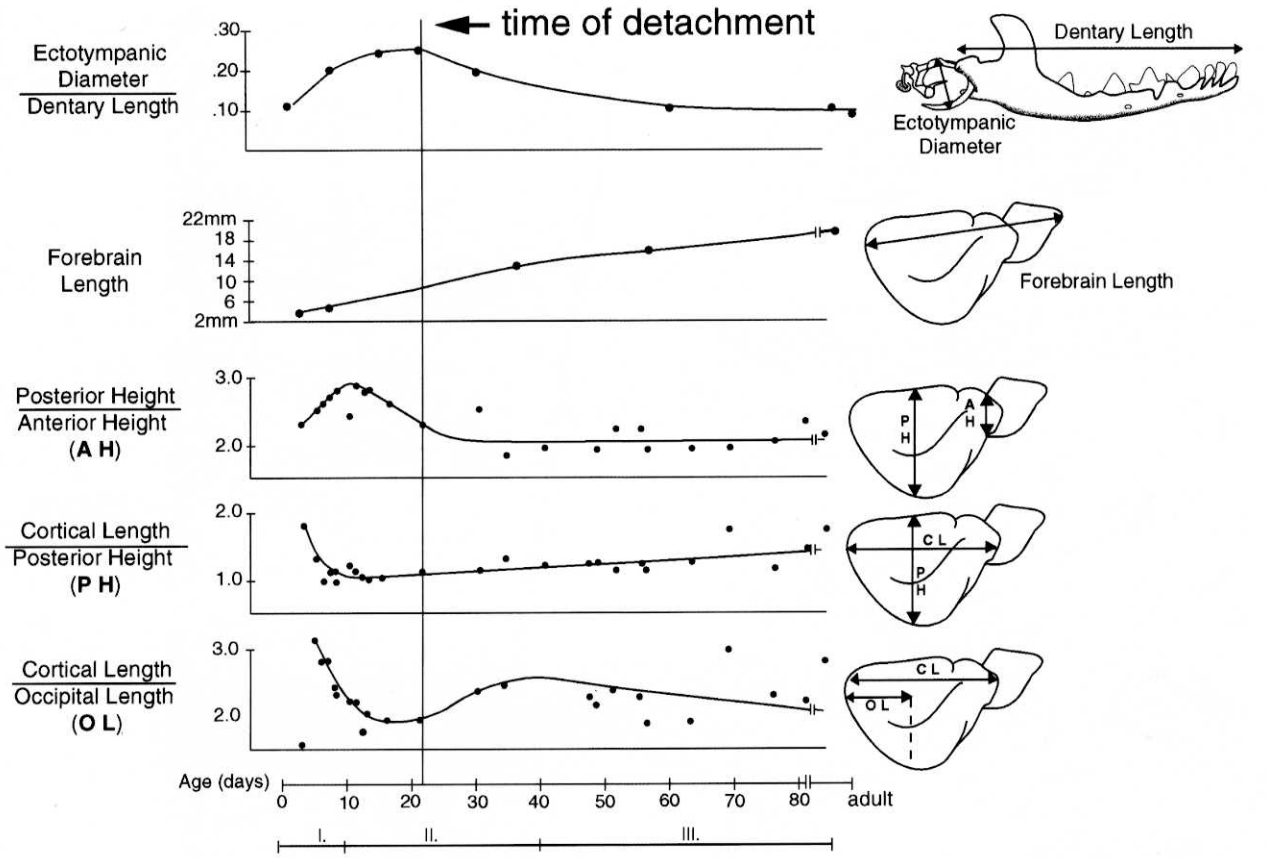

FIGURE 10. Differential growth of the forebrain (based on *Didelphis*, after Ulinski, 1971) and ectotympanic (based on *Monodelphis*). In the top graph, growth of the diameter of the ectotympanic is plotted as a function of the length of the mandible. In the second graph, growth of the total combined length of the olfacctory bulb plus cortex is plotted as a function of age. In the lower three graphs, relative growth of the different parts of the cortex is plotted as a series of ratios defined by the dimensions depicted on the mature brain. The ratios show a phase of ventro caudal growth (days 0–10), a phase of anterior growth (days 11–40), and a phase of occipital growth (days 41–81). From Rowe (1996).

12). At birth, the fenestra vestibuli lies immediately behind and medial to the CMJ, in a relationship similar to that found in adult *Morganucodon* and *Thrinaxodon*. The fenestra vestibuli and CMJ both lie external to the developing cerebral vesicle, along roughly the same "latitude" of cerebral circumference, which I refer to informally as the cortical "equator" (Fig. 11). As the brain grows, the magnitude of curvature of equator grows as well. The distance between the fenestra vestibuli and the CMJ, which both lie on the equator, also increases. The entire rear part of the skull appears to be pushed backwards from the facial skeleton and mandible by the growing brain.

The equatorial segment between the fenestra vestibuli and the CMJ defines an *arc of detachment* (Fig. 12) whose magnitude of curvature expands as the brain grows. As curvature of the *arc* expands, the fenestra is displaced progressively backwards. For about the first three weeks, the ear ossicles grow at a sufficient pace to keep up with the growing *arc*, thus maintaining their primitive linkage between the fenestra vestibuli and the mandible. As the ossicular growth rate slows and shifts into negative allometry, the brain continues its pace of growth for nine additional weeks and undergoes a ten-fold increase in volume during that time (Ulinski, 1971). During this time the *arc* nearly doubles in curvature, bursting the primitive arcade of skeletal elements that had spanned from the mandibular symphysis to the fenestra vestibuli. The middle ear bones maintain their attachment to the fenestra vestibuli and follow its trajectory backwards from the time of their detachment at the end of the third week until the brain stops growing in the twelfth week.

The timing of detachment prevents the disruption of function in the middle ear bones because it occurs before the onset of auditory functionality. The ear is unresponsive to sound until the 6th week and only thereafter does the auditory tract become myelinated (Langworthy, 1928; Larsell et al., 1935; McCrady et al., 1937; McCrady, 1938; McClain, 1939). The geometry of the widening *arc of detachment* accounts for the detachment of the auditory chain, for the precise path of its subsequent posterior displacement, and for the timing and extent of this movement in both ontogeny and phylogeny.

Discussion

The phylogenetic concordance of the inflated brain and the cranial ear implied the unexpected possibility of a causal

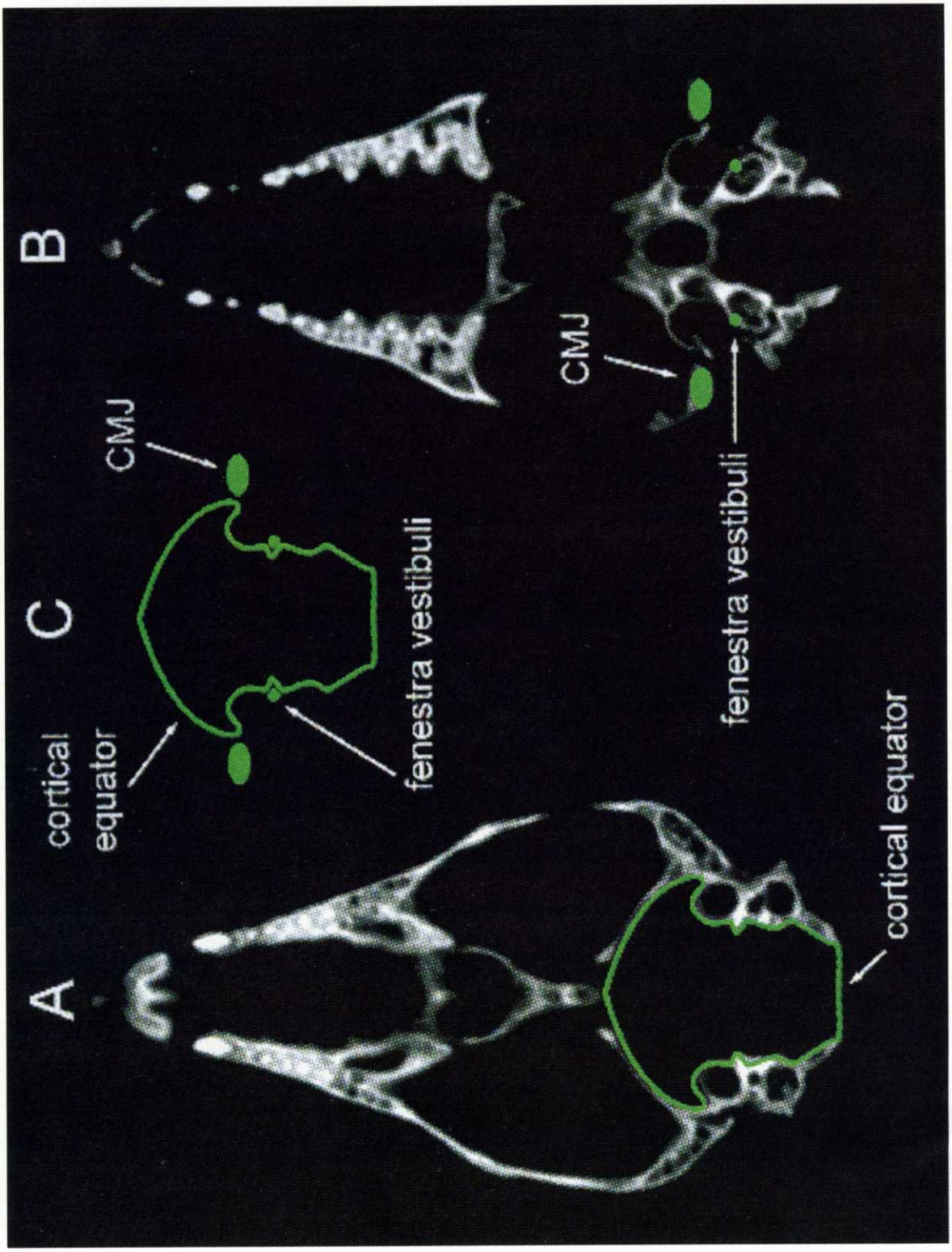

FIGURE 11. Landmarks for measuring brain growth. A) Transverse CT sections through the braincase at the greatest lateral width of the cortex, showing the slice plane used to illustrate the *cerebral equator* in Figure 12. B) section through the glenoid fossa and fenestra vestibuli (left). C) In the center, the positions of the CMJ and fenestra vestibuli are positioned relative to the cerebral equator. Individual slice thickness is 100 μ; slices A and B are 500 μ apart. CT imagery from Rowe (in press).

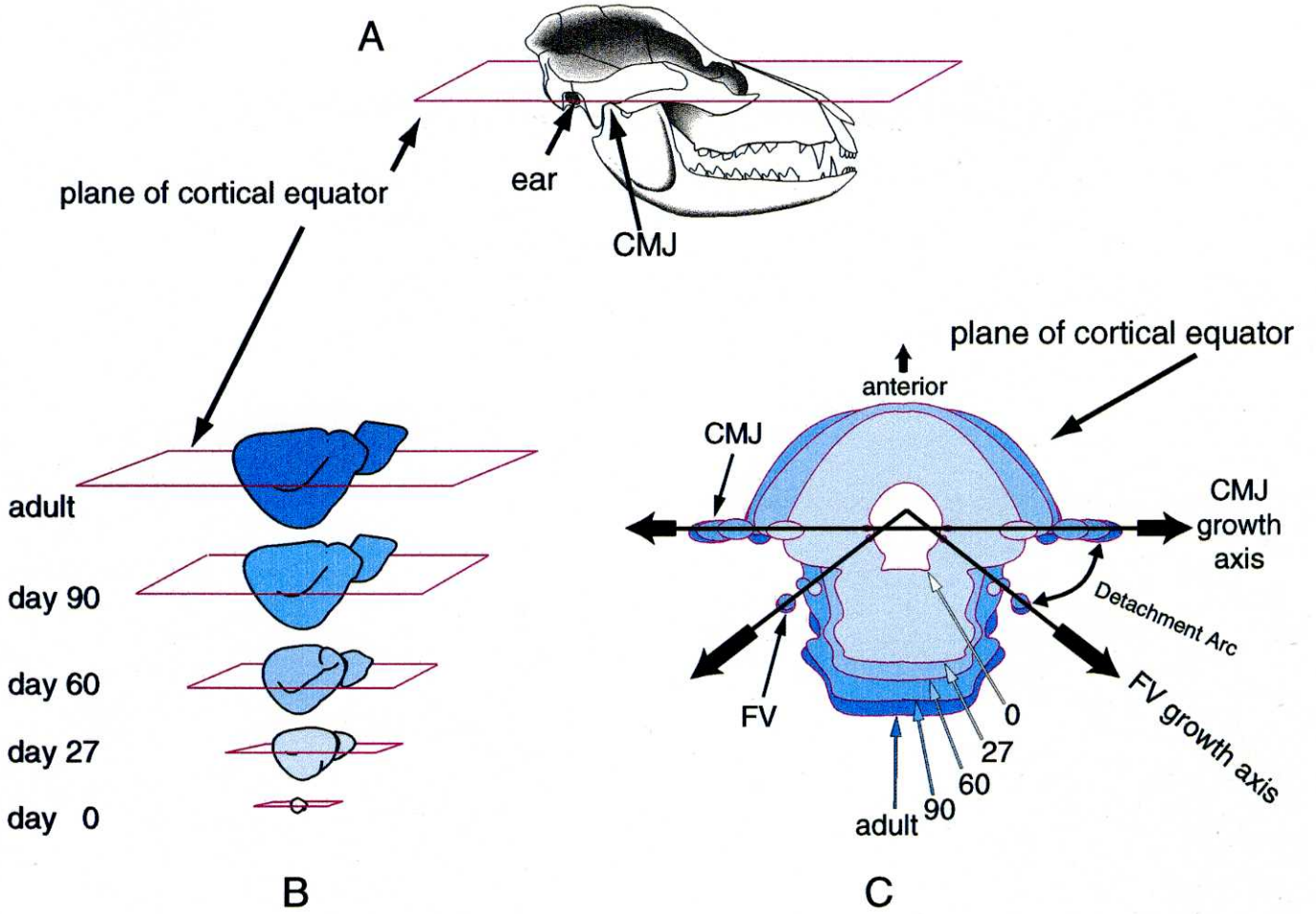

FIGURE 12. A) Location of a 1 mm-thick slice crossing the cerebral equator, fenestra vestibuli, and glenoid across the skull of a didelphid. B) Growth of the forebrain showing location of cortical equator. C) Superimposed cerebral equators of *Monodelphis* from day 0, day 27, day 60, day 90 and adult, relating the growth trajectories of the cerebral equator, fenestra vestibuli, and CMJ. Equatorial profiles taken from high resolution X-ray CT imagery of *Monodelphis*. From Rowe (1996).

relationship between the two structures, and this relationship appears to be corroborated by their ontogeny. The negative allometry of the auditory chain in the wake of continued rapid growth of the brain combine to cause the auditory chain to be detached from the mandible and carried backwards to its mature position behind the mandible. This new relationship originated in mammals ancestrally in an episode of heterochronic increase in rate and duration of brain growth. This one mechanism appears primarily responsible for both the evolutionary origin of the mammalian middle ear and its recapitulation in ontogeny. If this interpretation is correct, an event of fundamental importance in the origin of mammals was a heterochronic perturbation of brain development. As the pace and duration of brain development reached the ancestral mammalian level, a cascade of secondary, epigenetic effects was unleashed that affected virtually all aspects of mammalian life history.

One class of cascading effects involves intrinsic features of the brain and the many functions it controls. The specification of mammalian cortical regions is largely epigenetic as it occurs following neurogenesis, while clones of cortical neurons mingle during subsequent development. Neurogenesis appears to produce a cortex that is initially uniform and that later differentiates into specific functional areas by intercellular interactions (Walsh and Cepko, 1992), a process occurring over a protracted period of postnatal ontogeny. In the newborn opossum, for example, the cortex is unlayered, and subsequent development of its external appearance over the next 10 weeks mirrors many aspects of histogenesis and architectonic differentiation occurring at the same time (Riese, 1945; Ulinski, 1971). The extended duration of cerebral ontogeny that arose ancestrally in mammals afforded the specification of many new structures and an increased capacity for learning, both neuromuscular and associative, which continues long after cerebral differentiation and growth have ceased. Specific changes in cortical circuitry arising with expansion of the mammalian brain are related predominantly to elaboration of sensory components and enhancement of motor control. Modality-specific sensory channels through the thalamus to the telencephalon, which

were probably present in amniotes ancestrally, became expanded in association with an extended range of auditory frequencies, enhanced olfaction, and with the sensory function of hair (Ulinski, 1986; Butler, 1994). Also distinctively mammalian are the development of corticospinal (palliospinal) pathways (Northcutt, 1984), and well-developed specific motor nuclei which receive afferents from the cerebellum or basal ganglia, project to specific restricted regions of the cortex, and are situated rostrally in the ventral half of the thalamus (Ulinski, 1986). Mammals are further characterized by divided optic lobes, development of the pons varolii, and elaboration of the inferior olive and pontine nuclei (Ulinski, 1986; Gauthier et al., 1988). These features collectively resulted in elaboration of the sensorimotor system to a degree surpassing all other vertebrates (Ulinski, 1986; Butler, 1994). The effects of this cortical elaboration are manifested during life history in functions ranging from the complex repertoire of mammalian oropharyngeal functions (Smith, 1992) to the maintenance of rhythmic respiratory movements associated with mammalian metabolism (Carpenter, 1976) to the diverse patterns of mammalian locomotion (Bramble, 1989; Bramble and Jenkins, 1993). Some of these functions surely extend into pre-mammalian history, but the marked increase in cerebral differentiation and volume that occurred in Mammalia ancestrally suggests a marked increase in functionality compared with the conditions in *Morganucodon* and more distant synapsids.

Another class of epigenetic cascade induced alterations in structures extrinsic to the brain, especially the adjacent connective tissues. The shift to a cranial middle ear is the most notable example, but virtually all parts of the skull and neck near the brain were also modified. The pattern of skeletal modification is complex, involving an interplay of reduction, loss, fusion, hypertrophy, and heterotopy of the components. Comparable patterns of complex change are manifested by a variety of developmental pathologies of the skeleton which are traceable to early perturbations of the mesenchymal tissues in which the skeleton differentiates and which can be traced to mutations of single genes (Grüneberg, 1963).

Because heterochrony and its secondary effects are impossible to identify without a phylogeny, it is not surprising that the effects of brain heterochrony on the mammalian skeleton were unrecognized under the phenetic Linnean view of early mammalian history. The assertions of convergent evolution and the lack of obvious adult biomechanical or physiological correlation between the middle ear and brain further obscured the relationship of ear morphology to cerebral growth. The discovery of this unsuspected relationship between the brain and ear illustrates the potential value of phylogenetic systematics to the many developmental and experimental disciplines within biology which now operate largely in the absence of a well-corroborated phylogenetic framework. Within such a framework, experimental manipulations of developing mammals can be designed to further test the relationship between genetic and epigenetic factors in ontogeny, and to elucidate the mechanisms of evolutionary change in the historical context in which they evolved.

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List of Abbreviations

als - alisphenoid
ang - angular
ar - articular
bas - basisphenoid
boc - basioccipital
co - cochlea
ec - endocranial cavity
f.v. - fenestra vestibuli
h - standardized height of endocranial cavity
ipa - interparietal
j - jugal
ld - lambdoidal crest
mas - mastoid region of petrosal
mx - rock matrix surrounding parts of *Thrinaxodon* skull
mx/ec - rock matrix in endocranial cavity
c - occipital condyle
opth - opisthotic
pa - parietal
pet - petrosal
pin - pineal foramen
ppr - paroccipital process
pr - promontorium of petrosal
pra - prearticular
q - quadrate
qj - quadratojugal
sag - sagittal crest
sang - surangular
sq - squamosal
st - stapes
tr - tympanic recess
tym - ectotympanic