Introduction

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There is little doubt that much of what we know in biological anthropology is based on the experimentation with and excavation, measurement, and analysis of mineralized tissues. From the earliest excavation and recovery of fossil primate specimens, anthropologists have routinely used comparative skeletal materials and particular features on those materials to classify human and nonhuman primate species and to infer evolutionary relationships. Although early studies of skeletal biomechanics were primarily done by anatomists and orthopedists, anthropologists adopted biomechanical principles to infer activity from the shape of bones and to make inferences about life histories and habitual behaviors in the early part of the twentieth century (Washburn, 1951; Ruff, 2008). Our current interpretation of human and nonhuman primate origins and evolutionary history is still based primarily on osseous traits, although genetic and genomic data are being effectively used to resolve phylogenetic relationships that have resisted consensus based solely on skeletal traits (e.g., Perelman *et al*., 2011; Meyer *et al*., 2016). Currently, anthropologists explicitly recognize that the development and evolution of mineralized tissues are intertwined, with changes in developmental processes serving as a basis for phenotypic change (e.g., Lovejoy *et al*., 1999; Chiu and Hamrick, 2002; Hlusko *et al*., 2004). Consequently, anthropologists have been early adopters of technologies and approaches from other disciplines (e.g., genome-wide association study (GWAS), quantitative trail locus (QTL) analysis, quantitative imaging, breeding experiments), and have contributed to the design of new methods to acquire and measure data pertaining to changing biomechanical properties and to ontogenetic change of mineralized tissues (e.g., Cheverud *et al*., 1983; Ruff and Hayes, 1983; Richtsmeier *et al*., 1992; Richtsmeier and Lele, 1993; Smith and Tompkins, 1995; Strait *et al*., 2005, 2007; Slice, 2007; Raichlen *et al*., 2015). The adoption of a developmental focus has helped to shift emphasis away from the anatomy and classification of particular skeletal traits towards questions pertaining to developmental processes that underlie the production of those traits and their variation (Hallgrímsson & Lieberman, 2008; Reno *et al*., 2008; Hallgrímsson *et al*., 2009; Young *et al*., 2010; Serrat, 2013; Kjosness *et al*., 2014; Reno, 2014; Rolian, 2014). In this way, anthropological analyses of skeletal remains have expanded from comparisons based on external features and metrics that are used to build phylogenies to the advance of approaches aimed at uncovering the developmental basis for variation in skeletal morphology and evolution. This book includes research conducted by a broad sample of anthropological researchers who are using their expertise to dissect the ways in which development of both the cranial and postcranial skeleton can be used to further our understanding of the basis of novel variation and the role that changes in developmental processes play in the evolution of skeletal morphology.

Because biological anthropological data sets have historically been principally skeletal in nature, anthropologists have always been favorable toward developing or adopting new technology and novel approaches to the analysis of skeletal tissues. During the twentieth century, investigators began to interrogate bone in new ways. Engineering principals as applied to bony architecture were codified by Wolff's law and anthropologists applied this law in the study of skeletal samples under the paradigm that bone is a living tissue that responds mechanically to stress and/or strain in ways that insure tissue strength and resistance to loads where it is needed. The patterns visualized in bone were interpreted as forming in response to mechanical loading. Wolff's law, and predictions stemming from it, were routinely used to check the relationship between lifestyle and bone architecture in living primate species and to propose the locomotory mode of recovered fossil species. However, further laboratory work showed that bone can have highly variable responses to similarly applied forces and that variations in the skeleton can derive from a complex mix of genetic and epigenetic influences (Pearson and Lieberman, 2004; Ryan and Shaw, 2014). Genetic history, sex, nutrition, diet, hormonal influences, life history, phylogenetic history, maturity, microstructural properties of a particular bone region, and body size comprise some of the additional factors that are found to contribute to the osseous response to applied forces. Mineralized tissues may be those most accessible to anthropologists, but the information they contain relating to life history, function and evolution might be harder to tease from inert and sometimes fossilized samples than once thought. Such realizations provided an impetus for the use of experimental animals by anthropologists where certain of these variables can be experimentally controlled and the influence of the others can be tested.

Bone is a living tissue whose characteristics, even within species, are highly variable in time and space. In the 1970s and 1980s, bioarcheologists began to take advantage of this variation to pose population-level questions of skeletal series. Skeletal remains came to be used as the primary data set of problem-oriented research aimed at the investigation of mortuary practice (e.g., Buikstra, 1981), disease vectors in paleopathology (e.g., Armelagos *et al.*, 2005; Wolfe *et al.*, 2007), population dynamics and paleodemography (e.g., Wood *et al.*, 1992), fracture healing (e.g., Boldsen *et al.*, 2015), and biological (genetic) relationships among populations (e.g., Buikstra *et al.*, 1990). In these applications, skeletal variation became the criterion upon which hypotheses pertaining to the sociocultural context of associated populations represented by the skeletal remains were tested. These approaches are the foundation of modern bioarcheology that recognizes the necessity of large sample sizes for understanding processes at the population level.

In addition to these important research directions that remain valid and currently in use, anthropologists have always shown an interest in the changing shapes of bones during growth and in the differences observed between immature and mature skeletons. Anthropologists have led the way in developing methods that tease more information from the bones than would seem evident at first glance. In the simplest examples, knowledge of the sequence of developmental events and how bone grows (e.g., the order and timing of closure of epiphyses and of cranial sutures, the changing morphology of bones throughout life) have enabled the aging of single skeletons and the analysis of population dynamics and demography when these data are available from samples of known provenience. More complex analyses of growth patterns using varied types of morphological data from varied skeletal tissues and multiple methods of analysis have been used to estimate the age of fossil specimens (e.g., Holly, 1992; Smith and Tompkins, 1995), to compare growth between species (e.g., Ackermann and Grovitz, 2002; Bastir and Rosas, 2004; Berge and Penin, 2004; Bulygina *et al.*, 2006; Bastir *et al.*, 2007; Boughner and Dean, 2008), to determine the influence of particular patterns of growth on known morphologies (e.g., Richtsmeier *et al.*, 1993), and to predict the morphology of "hypothetical forms" by mathematically applying estimated growth trajectories to given morphologies (e.g., Richtsmeier and Lele, 1993; McNulty *et al.*, 2006). These approaches have largely been based on what could be coaxed from measured morphological changes associated with bone growth, namely change in size and shape. More recently, anthropologists have been able to use advanced imaging technologies to study important morphological indicators of growth at much smaller scales, develop novel methodologies for their use in the study of populations, and derive new knowledge from these observations. The field of genetics has also become increasingly relevant to the anthropological study of phenotypes and their growth. Not only does knowledge of the genetics of bone development inform us of how bone is formed (e.g., Long, 2012), but correlations between specific genetic variants and variation in quantitative skeletal traits over developmental time point to the contribution of genetic variation to variation in skeletal phenotypes. For example, Hager and colleagues (2009) conducted a series of quantitative trait loci experiments to identify genomic regions that affect body size growth processes revealing that distinct genomic regions affect early postnatal growth (1–3 weeks) while others affect later growth (4–10 weeks) (Hager *et al.*, 2009).

With the advent of evolutionary developmental biology, additional experimental tools, laboratory methods, and genetic approaches became available to anthropologists interested in determining the developmental basis for evolutionary change within the fossil record and phylogenetic differences between living species. Approaches developed within the emerging field of evolutionary developmental biology (evo–devo) enabled the characterization how change occurring within developmental programs is fundamental to evolutionary processes (Carrol *et al.*, 2001). Evo–devo encompasses research on how variation in development relates to the evolutionary changes that occur between generations. Early traces of the evo–devo perspective can be found in the work of, for example, Bonner (1982), Gould (1977), Waddington (1942), and De Beer (1940), but the molecular revolution that occurred in the last decade of the twentieth century made a new set of tools and resources (e.g., increasingly accessible sequencing technology; increasing computational power; novel immunohistochemistry assays; increased understanding of the complexity of the genome) potentially available to anyone with an interesting question pertaining to the mechanisms that link the genotype with the phenotype and how change measured within a single generation relates to change across many generations.

Although first developed and widely used in other disciplines, resources including specific reagents, transgenic technologies, techniques for gene editing (e.g., CRISPR), genomic sequencing, and genotyping and biological imaging technologies, have become increasingly available at diminishing cost. The traditional training offered in anthropology graduate programs meant that, at their introduction, few anthropologists were appropriately trained to adopt and apply these tools. Thankfully, there were investigators from other disciplines with the appropriate expertise who were eager to work on anthropological problems and to work collaboratively with anthropologists on subjects pertaining to human evolution. These collaborative beginnings, followed by a rapid increase in the number of biological anthropologists seeking training in these techniques, prompted a maturation of the field that is now evident in many aspects of biological anthropology. For example, while the relevance of experimental studies in mice in studies of human evolution was openly questioned only 20 years ago, it is now commonplace for anthropologists to propose and test hypotheses about human and nonhuman primate growth, development and evolution using data from non-primate animal models. The amazing number of genomes now sequenced, along with emerging knowledge of the evolution of genomes, enables an even more direct connection of human biology with fish, mammal and chick biomedical models, illuminating the relevance of distantly related species to understanding the evolution of human developmental processes and the function of human regulatory sequences (see, for example, Lamason *et al.*, 2005; Braasch *et al.*, 2016).

These new research trends in anthropology have not occurred due to a directed reorganization of the discipline, but instead represent an organic expansion of the field of biological anthropology as scientists observe what is happening in the larger world of biological research and imagine how they might apply those technologies and skill sets to anthropologically inspired research questions. Bridges have always existed across the subfields of anthropology (biological, cultural, and archeology traditionally, and more recently with ecological, forensic, and genetic anthropology), but connections between biological anthropology and other disciplines are creating collaborative links that previously would have seemed incongruent. These relationships serve as the foundation for necessary changes in anthropological training programs and independent research projects that welcome the incorporation of methods, knowledge, and perspectives from outside of anthropology. The push towards collaborative, cross-disciplinary research in many universities is evident in the chapters presented in this book, and we hope that this volume helps to create and inspire additional connections within the field and across disciplines by exposing anthropologists to a variety of new perspectives in the study of bone development.

The diverse training becoming progressively available to students of biological anthropology provides new knowledge for those eager to translate observations of lifeless skeletal remains into hypotheses that concern behavioral, molecular and morphological evolution, mechanisms of osseous development, and the relationship between organisms and their environment. These new opportunities enable anthropologists to expand their work from theory-driven analyses of skeletal features to experimental approaches that are aimed at revealing biological mechanisms that underlie phenotypic changes evidenced in skeletal remains. Developmental biology, evolutionary developmental biology, genetics and genomics are probably the fields that have contributed most to the changing world of biological anthropology research, and our chapters reflect that contribution. However, the influence of other disciplines is also apparent in this volume, and it would be premature to predict which fields will provide important discoveries and collaborative inputs in the future. Because anthropologists are trained broadly to consider problems pertaining to human evolution, they often can make connections that might be missed by people working in other fields. The challenge for current and future generations of anthropologists is to maintain this broad perspective *and* obtain adequate training in their chosen area of specialization including becoming proficient in necessary technological, computational and/or laboratory skills while resisting the impulse of becoming overspecialized.

This book presents explicit examples of cross-disciplinary research in biological anthropology with the uniting principle of a focus on early formation and growth of bone, the tissue most often left behind in paleoanthropological and archeological contexts. Although the book is organized according to studies that focus on the appendicular versus axial skeleton, many of the chapters focus on fundamental issues that could apply to either part of the skeleton. Our volume starts with an introductory and historical perspective from **Ken Weiss**. By asking the question "What is a biological trait?" this chapter provides important observations of both theoretical and practical concern by considering the genetic basis for traits like those that have been used by biological anthropologists to assign specimens to a taxon. The development of these traits is complex and this complexity must be acknowledged when attempting to understand the production of these phenotypic traits from genetic information. What besides the genetic information that can be tabulated contributes to the morphology produced? What role do those additional components have? And what, in reality, is a complex trait?

The chapter by **Christopher Percival and Joan Richtsmeier and colleagues** provides a brief review of processes underlying skull formation and development, followed by the description of primary research in a mouse model that helps to illuminate the role that blood vessels play during craniofacial osteogenesis. The results of this work suggest ways in which dysregulation of the relationship between blood vessels and bone might contribute to variation within and between extant primate species, while also illustrating how the quantification of multiple aspects of craniofacial skeletal phenotypes can provide a more complete understanding of how genetic changes modify osteogenesis in the skull. While existing biomedical models can be leveraged to develop a more complete understanding of potential developmental bases for evolutionary change in the skull, anthropologists and evolutionary biologists must take the lead in applying these models to evolutionary questions because researchers interested in disease will not.

Kazuhiko Kawasaki and Joan Richtsmeier present a detailed embryological description of the anatomy of the chondrocranium: that part of the endoskeleton that protects the brain and three principal sense organs but does not include the pharyngeal endoskeleton. After years of studying the genetic basis of bones and teeth (Kawasaki) and the morphology and growth of the mammalian skull (Richtsmeier), these authors provide precise definitions and detail the distinction between the cranial base and the chondrocranium. To provide definitions that are based on the evolution of the endoskeleton and dermal skeleton, these authors combine developmental, evolutionary, and anatomical approaches in the analysis of cranial evolution, and use embryological observations of the laboratory mouse to define the chondrocranium and the dermatocranium and the coordinated development of these structures. Finally, the authors use data relating to the spatiotemporal associations of the chondrocranium and dermatocranium to suggest their dynamic interaction during skull formation and suggest implications for understanding cranial modularity and integration.

Postorbital septation in primates has long been a morphological trait of interest. **Valerie DeLeon, Alfred Rosenberger, and Tim Smith** describe the unique ontogenetic patterns of postorbital septation in tarsiers and apply their findings to the question of trait homology to show how ontogeny of skeletal elements can provide evidence of phylogenetic relationships. Using a comparative ontogenetic approach, the authors show that early postnatal tarsier orbits show ontogenetic adaptations that delay osseous closure of the orbital fossa to allow eye enlargement, followed by the development of an osseous septum that serves to support the overly large eye. The authors conclude that postorbital septation in tarsiers is secondary to eye hypertrophy. Based on this conclusion, they propose possible scenarios for the evolution of septation in tarsier and anthropoid lineages and emphasize the importance of ontogenetic continuity in evaluating hypotheses about trait homology.

In a chapter about facial shape change during growth, **Sarah Freidline, Cayetana Martinez-Maza, Philipp Gunz, and Jean-Jacques Hublin** combine data pertaining to patterns of bone modeling (formation and resorption fields on the face and mandible) and morphometric measures of facial shape and form in an attempt to understand the correspondence between large-scale morphological shape changes and bone modeling patterns at a microstructural level. These investigators characterize the size and shape of a cross-sectional ontogenetic sample of human skulls of various ages whose patterns of facial bone formation and resorption fields were previously mapped to investigate whether or not these two types of data can be combined to create informative growth models. Interesting observations pertaining to the correspondence in patterns of variation at both the microscopic and macroscopic levels of analysis are provided.

Paul Dechow uses a unique human and porcine data set to show how cortical bone material properties can be used to reveal changing complex biomechanical properties of individual bones during ontogeny. This valuable and informative data set provides a first glimpse at the potential regularities of the ontogeny of bone material variation within humans and pigs and enables hypothesis-building about these properties across species. The implications of this study provide novel evidence that analyses of bone function and evolution that are limited to a purely structural–mechanical approach can lead to uninformed conclusions about adaptation. Dechow uses the mandible in this study, a skeletal element that is both widely studied and whose loading patterns are adequately known, so these results might be corroborated across additional species in the future. Dechow's observations also lay the ground work for studies of variation in such properties that could represent evolutionary adaptations to unique craniofacial functions or patterns of development.

David Burr and Jason Organ offer a comprehensive review of endochondral growth of long bones and synovial joints with the goal of revealing how changes in patterns of skeletal growth and development drive morphological change evidenced in the evolution of the postcranial skeleton. The authors discuss the influence of postnatal physiologic adaptions on the size and shapes of joints and how these are constrained by evolution. A discussion of the relative contributions of mechanical environment and genetic and epigenetic mechanisms to the evolution of limb bone morphology, especially joint morphology, provides insight into the physiologic adaptations that are primarily mechanical, but also thermoregulatory, hormonal and dietary, and lead to change in bone shape. The authors show how these influences operate within an evolutionary template and how small changes in genetic or epigenetic regulatory mechanisms contribute to change in bone shape during growth and during evolution.

Terence Capellini and Heather Dingwall discuss our current lack of knowledge about the genotypes that underlie phenotypic variation in primate skeletal morphology. Because most genes have pleiotropic effects and complex traits are known to have a polygenic basis rather than being controlled by a single locus, gaining knowledge of the mechanisms that bridge genotype and phenotype presents a formidable challenge. Using appendage skeletal development as their example, Capellini and Dingwall provide a timely and insightful guide to the genetic, molecular, and developmental tools that are available to the anthropologist interested in filling in gaps along the genotype–phenotype continuum in the context of primate skeletal variation and evolution. The authors show that understanding the inherited basis of morphological variation requires the coordinated application of cutting-edge experimental techniques in genetics, functional genomics, and developmental genetics. In this context, the authors provide guidance on how advances in genetics help to identify and connect a genetic locus to variation in skeletal morphology, whereas novel functional genomics tools help to sift through the numerous genetic variants within an associated locus for putative variants responsible for changes in a species-specific phenotype. Finally, the use of novel developmental biology tools provide for a direct assessment of the functional causality of an identified sequence to reveal molecular mechanisms and their impacts on the development of a phenotype. They reveal that the combined use of data sets generated from the most recent advances in each of the above fields allows researchers to identify the causal genetic variants the control variation, and the likely mutations that natural selection has acted upon to sculpt skeletal morphology in primates.

Kelsey Kjosness and Phil Reno provide a complete description of growth plates and how work with knockout murine models has greatly expanded our understanding of growth plate design and function. The authors demonstrate the differences between growth of bones of the hands and feet and growth of long bones of the limbs, the latter being most commonly studied by those interested in skeletal growth. They take advantage of this normal variation in endochondral ossification to identify mechanisms of growth plate development. First, therian mammal metapodials and phalanges form a single growth plate at only one end, while typical long bones form a growth plate at both ends. Second, the mammalian pisiform and calcaneus are unique among the bones of the wrist and ankle in forming a growth plate. The authors take advantage of this situation in the developing mouse, where skeletal development and growth plate biology can be queried experimentally during prenatal growth to analyze patterns of chondrocyte proliferation and explore the expression of specific genes to growth plate formation. Using further comparisons with metatarsal formation in alligators, which still form a growth plate at each end of the bone, the authors provide information pertaining to the association between the expression of the Indian hedgehog receptor, Patched, and patterns of cellular proliferation that distinguish growth plate forming and non-forming sites. In addition, Hox genes are hypothesized to be fundamental to growth plate formation, a view supported by their reduced expression in the developing wrist and ankle which generally lack growth plates. The authors demonstrate the expression of *Hoxd11* adjacent to the growth plate containing pisiform in the wrist as further evidence for the important role of Hox genes in growth plate formation. These authors provide a valuable example of how the identification of these types of patterns in model and non-model organisms can be used to discover and affirm the evolution of growth mechanisms responsible for phenotypic variation.

Ian Wallace, Brigitte Demes, and Stefan Judex provide a useful description of bone responsiveness to mechanical signals, from the molecular to organ level, in order to provide context for a consideration of the non-genetic factors (age and genetic background) that contribute to bone mechanoresponsiveness. There is a huge anthropological literature in which functional loading history of organisms known only by their skeletal remains is inferred from what is known from work with experimental animals (mostly laboratory mouse) and studies of humans. By focusing on what is known of the genetic and ontogenetic influence on bone mechanoresponsiveness in humans, these researchers demonstrate that the primary basis for variation in bone structure is youth physical activity, even in the bones of adults. In addition, the significant influence of genetic background on mechanoresponsiveness means that multiple species or populations may exhibit different degrees of structural evidence for the same activities. These observations indicate additional complications when interpreting loading history from morphological studies of bone, but provide an impetus to broaden our perspective on mechanobiology and scope of inquiry when studying functional skeletal morphology.

Russ Hogg, Tim Bromage, Haviva Goldman, Julia Katris, and John Clement explore the relationship between oscillations in the sympathetic nervous system and growth increments visible in mineralized tissue to try to uncover a circadian mechanism that leads to histologically identified bone growth increments. Specifically, the biorhythm known as Havers–Halberg oscillation (HHO), is expressed as growth increments in mineralized tissues in various forms; e.g., lamellae in bone, and striae of Retzius in dental enamel. The authors review the relationships among bone formation, neuroendocrine physiology, and bone metabolism aimed at relating these subjects to long-period rhythms in bone and teeth, and ultimately to mammalian life history evolution. The authors hypothesize an important role for HHO cycles in the evolution of life history traits among primates and suggest that associated patterns of bone remodeling can be used to estimate life-history characteristics of skeletal and fossil specimens.

Tim Ryan, David Raichlen, and James Gosman emphasize the impact of age and ontogeny on variation in skeletal mechanical responsiveness in a study of changes in the humeral and femoral metaphyses of human juveniles. These authors use computed tomography images to estimate three-dimensional trabecular bone structural features and determine the difference in these features as individuals age. This study shows the difference in trabecular bone architecture of these two bones throughout growth. Femoral measures show patterns that are significantly correlated with age, but measures in the humerus, whose role in bipedality is quite different, do not. Given that the differences between femoral and humeral metaphyseal trabecular bone architecture develop only after the onset of walking in children, the authors suggest that these architectural patterns directly reflect the divergent loading regimes experienced by these two skeletal regions.

Although they are quite diverse, these chapters represent some of the most advanced approaches to the study of bone development by leading anthropologists, and illustrate how these new avenues can inform evolutionary research. In combination, the chapters of this volume provide a snapshot view of the discipline at the time of publication and links work by researchers with different perspectives on bone growth and development, fostering cross-disciplinary dialogue and encouraging collaborative research.

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