Mineralized Tissues in Oral and Craniofacial Science
Biological Principles and Clinical Correlates
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The idea for this book was conceptualized in 2009, at an annual American Academy of Periodontology meeting in Boston, which we were invited to present a continuing education symposium on mineralized tissues. Specifically, we were asked to gear our presentations to relevance for practitioners. The session was well attended and the audience was clearly interested in grasping the underlying biology of mineralized tissues of the dental-oral-craniofacial apparatus, yet with application to clinical scenarios. After the symposium and a long discussion while walking the streets of Boston, along with numerous phone calls and e-mails, the goals and objectives of this work took shape, and the colleagues who agreed to join and provide their valuable knowledge and experience made the project feasible.

The broad objective of this book is to provide a comprehensive update on knowledge in the field of mineralized tissues, focusing on the dental-oral-craniofacial region and including clinical correlates that reinforce the significance of the scientific knowledge to clinical diagnoses and therapies. Basic science chapters are followed with at least one correlate chapter of clinical relevance (i.e., case studies). To ensure a link between these, the basic and clinical correlates follow a general schematic that was largely utilized by all authors. All figures are digitized and downloadable for presentation purposes. Clinical case studies are described in a manner that lends easily to their use in teaching venues.

This original approach, linking the basic principles of hard-tissue cell and molecular biology to clinical correlates, aims to attract a diverse audience, both students and faculty, including those at early stages of their research career, as well as more senior faculty interested in a comprehensive text for reference. Moreover, by providing clinical correlates, this text will appeal to non-dental faculty and students by providing additional insights to the translational aspects of their research and also as an important reference source for students in a wide variety of healthcare programs. Finally, we anticipate interest in the textbook on the part of all health care providers who seek to understand the underlying biology of mineralized tissues they treat daily in their practice. With the exponential growth of scientific information, there is a greater need than ever before to make sure that the research communities are updated on the most current findings in all areas of science. At present, there is no comprehensive review of the topics presented here (i.e., one focusing specifically on hard tissues of the oral cavity). Equally important is the link of basic principles to clinical situations. More than ever before, as we are confronted with discoveries resulting in increasingly complex issues in science, there is a need for collaborative efforts across all disciplines in order to reach our ultimate goal of improving the quality of life for all in our community.

We enjoyed the development and orchestration of this volume tremendously. Our author colleagues were wonderfully responsive and ardently involved in their chapter contributions. The joining together of colleagues from all over the world and in all facets of this subject was highly rewarding, and we truly hope the readers will appreciate the depth and breadth this work provides.

Laurie K. McCauley
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We would like to express our appreciation to the dedicated author contributors of this book for their enthusiasm toward the approach taken to link the basic biology with clinical practice and for their shared expertise and meticulous and timely efforts to bring this to fruition. Special thanks go to Norman Schiff for coordinating the authors, making sure manuscripts were received in a timely fashion, and for his patience along the way; to Jessy Grizzle for being a publishing role model and ever patient spouse; to Dr. Erika Benarides for the CT cover image; and to Kathy Ribbens for her assistance in editing and preparing the complete initial draft. Finally, we would like to thank the publishers for engaging in our vision to develop a book that will serve the community of scientists, scholars, teachers, clinicians, and students who seek expert information regarding craniofacial skeletal health and disease.

L.K.M.
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When solid research blends with clinical application: a book for a diverse audience emerges

The craniofacial skeleton provides critical protection for the neural system and houses our precious sensory organs of sight, sound, smell, and taste. Teeth comprised of three unique mineralized tissues are supported by bone, a fourth distinct tissue. Each of these tissues has a very unique molecular and biologic profile. Bones of the oral cavity are impacted by a wide variety of infectious agents, are subject to unique biomechanical forces, and are highly responsive to environmental stresses. Virtually all of these topics are covered in this new book, edited by two preeminent clinician scientists. The subject matter is presented with a focus and depth consistent with a rigorous scientific periodical. Importantly, information is not presented in isolation, but instead flows seamlessly with excellent integration and connection to systemic interactions and clinical implications.

This new body of work orchestrated by Drs. McCauley and Somerman brings together 85 outstanding contributors from 13 countries in 39 chapters that cover all the relevant aspects of mineralized tissues pertinent to oral and craniofacial biology in health and disease. A review of the developmental, molecular, and cellular aspects of bones and teeth sets the framework for this volume. The expert basic science reviews are enhanced further by including relevant clinical examples that speak to the strong translational focus of this book. This book will provide readers with basic tenets, recent advances, and meaningful links that impact patient care. A wide audience will benefit, including those already established in the field, new investigators, students, dental clinicians, and health care professionals in complementary areas such as endocrinology, rheumatology, orthopedics, and pediatrics, among others. We fully anticipate that this book will represent a landmark contribution to the field and set a new standard for many years to come.

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SECTION 1

Bones of the oral-dental and craniofacial complex
In this chapter, we provide a general overview of embryological events pertinent to the development of the bony structures of the craniofacial complex, which has been largely adapted from Ten Cate's *Oral Histology Textbook* (Nanci 2007). We also briefly review well-established molecular concepts at play in craniofacial patterning and some of the more recent developments in this field. In this context, processes have been abridged and only detailed when necessary for logical flow. For a more comprehensive treatise, readers are referred to this chapter’s references.

The cranial region of early jawless vertebrates comprised (1) cartilaginous elements to protect the notochord and the nasal, optic, and otic sense organs (neurocranium); and (2) cartilaginous rods supporting the branchial (pharyngeal) arches in the oropharyngeal region (viscerocranium). Together, the neurocranium and the viscerocranium formed the chondocranium. As vertebrates evolved, they came to develop jaws through modification of the first arch cartilage, with the upper portion becoming the maxilla and the lower portion the mandible. In addition, they acquired larger sensory elements resulting in a significant expansion of the head region. Bony skeletal elements (the dermal bones), evolved for protection, formed the vault of the skull and the facial skeleton that included bony jaws and teeth. The cephalic expansion required a new source of connective tissue that was achieved by the epitheliomesenchymal transformation of cells from the neuroectoderm. Indeed, the neural origin of craniofacial bones distinguishes them from other skeletal bones, and may, in part, explain why in certain cases bones at these two sites are differentially affected (e.g., osteoporosis). Comparison between the cranial components of the primitive vertebrate skull and the cranial skeleton of a human fetus is shown in Figure 1.1.

### Head formation

Neural crest cells (NCCs) from the midbrain and the first two rhombomeres transform and migrate as two streams to provide additional embryonic connective tissue needed for craniofacial development (Figure 1.2). The first stream provides much of the ectomesenchyme associated with the face, while the second stream is targeted to the first arch where they contribute to formation of the jaws. NCCs from rhombomere 3 and beyond migrate into the arches that will give rise to pharyngeal structures. Since homeobox (Hox) genes are not expressed anterior to rhombomere 3, a different set of coded patterning genes has been adapted for the development of cephalic structures. This new set of genes, reflecting the later development of the head in evolutionary terms, includes the Msx (muscle segment Hox), Dlx (distal-less Hox), Barx (BarH-like Hox) gene families.

### Branchial arches and formation of the mouth

The mesoderm in the pharyngeal wall proliferates, forming as six cylindrical thickenings known as branchial or pharyngeal arches. Four of these arches are major; the fifth and sixth arches are transient structures in humans. The arches expand from the lateral wall of the pharynx toward the midline.

The inner aspect of the branchial arches is covered by endoderm (with the exception of the ectoderm of the
At about the middle of the fourth week of gestation, the first branchial arch establishes the maxillary process, so that the oral cavity is limited cranially by the frontal prominence covering the rapidly expanding forebrain, laterally by the newly formed maxillary process, and ventrally by the first arch (now called the mandibular process; Figure 1.3).

**Formation of the face, primary palate, and odontogenic epithelium**

Early development of the face is dominated by the proliferation and migration of ectomesenchyme involved in the formation of the primitive nasal cavities. At about 28
The maxillary process fuses with the lateral nasal process to form the lateral wings of the nose and cheek areas. The face develops between the 24th and 38th days of gestation. As fusion of facial processes occurs, the epithelium on the inferior border of the maxillary and medial nasal processes and the superior border of the mandibular arch begin to proliferate and thicken. These thickened areas will soon give rise to an arch-shaped continuous plate of odontogenic epithelium on both the maxilla and the mandible.

Formation of the secondary palate

Initially, there is a common oronasal cavity bounded anteriorly by the primary palate. The subsequent development of the secondary palate creates a distinction between the oral and nasal cavities. Its formation commences between seven and eight weeks and completes around the third month of gestation. Three outgrowths appear in the oral cavity: the nasal septum grows downward from the frontonasal process along the midline, and two palatine shelves, one from each side, extend from the maxillary processes toward the midline. The
septum and the two shelves converge and fuse along the midline, thus separating the primitive oral cavity into nasal and oral cavities. As the two palatine shelves meet, adhesion of the epithelia occurs. The epithelial cells at the seam undergo epitheliomesenchymal transformation, and they acquire mesenchymal characteristics and the ability to migrate, thus establishing continuity between the fused processes. The closure of the secondary palate proceeds gradually from the primary palate in a posterior direction.

**Development of the skull**

The skull can be divided into three components: the cranial vault, the cranial base, and the face (Figure 1.5). Membranous bone forms the cranial vault and face while the cranial base undergoes endochondral ossification. Some of the membrane-formed bones may develop secondary cartilages to provide rapid growth.

Intramembranous bone formation was first recognized when early anatomists observed that the fontanelles of fetal and newborn skulls were filled with a connective tissue membrane that was gradually replaced by bone during the development and growth of the skull. During this process, ectomesenchymal cells proliferate and condense at multiple sites within each bone of the cranial vault, maxilla, and body of the mandible. At these sites of condensed mesenchyme, osteoblasts differentiate and begin to produce bone. This first embryonic bone forms rapidly and is termed woven bone. At first, the woven bone takes the form of spicules and trabecules, but progressively these forms fuse into thin bony plates that may combine to form a single bone. In general, there is resorption on endosteal surfaces and bone formation on periosteal ones. However, depending on adjacent soft tissues and their growth, segments of the periosteal surface of an individual bone may contain focal sites of bone resorption. For instance, growth of the tongue, brain, and nasal cavity and lengthening of the mandible body require focal resorption along the periosteal surface.

![Figure 1.4](image1.png)

*Figure 1.4* Scanning electron micrograph (SEM) of a human embryo at around six weeks. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

![Figure 1.5](image2.png)

*Figure 1.5* Subdivisions of the skull. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)
Conversely, segments of the endosteum of the same bone simultaneously may become a forming surface, resulting in bone drift. Woven bone of the early embryo and fetus turns over rapidly. There is a rapid transition from woven bone to lamellar bone during late fetal development and the first years of life.

As fetal bones begin to assume their adult shape, continued proliferation of soft connective tissue between adjoining bones brings about the formation of sutures and fontanelles. Sutures play an important role in the growing face and skull. Found exclusively in the skull, sutures are the fibrous joints between bones. However, sutures allow only limited movement. Their function is to permit the skull and face to accommodate growing organs such as the eyes and brain.

The periosteum of a bone consists of two layers: an outer fibrous layer and an inner cellular or osteogenic layer apposed to the surface of the bone. At sutures, the outer fibrous layers of the two adjacent bones involved in the joint extend and fuse across the gap between the bones. The osteogenic layer and part of the fibrous layer of each bone run down through the gap between the bones. When these are forced apart, for example by the growing brain, the structural arrangement at the suture allows bone formation at the margins while keeping the bones separated yet strongly tied together.

Endochondral bone formation occurs at the articular extremity of the mandible and base of the skull. Early in embryonic development, a condensation of ectomesenchymal cells occurs. Cartilage cells differentiate from these cells, and a perichondrium forms around the periphery, giving rise to a cartilage model that eventually is replaced by bone.

**Development of the mandible and maxilla**

As indicated above, the mandible and the maxilla form from the tissues of the first branchial arch, the mandible forming within the mandibular process and the maxilla within the maxillary process that outgrows from it.

**Mandible**

The cartilage of the first arch (Meckel’s cartilage) forms the lower jaw in primitive vertebrates. In human beings, Meckel’s cartilage has a close positional relationship to the developing mandible but is believed to make no direct contribution to it. At six weeks of development, this cartilage extends as a solid hyaline cartilaginous rod surrounded by a fibrocellular capsule from the developing ear region (otic capsule) to the midline of the fused mandibular processes (Figure 1.6). The two cartilages of each side do not meet at the midline but are separated by a thin band of mesenchyme.

On the lateral aspect of Meckel’s cartilage, during the sixth week of embryonic development, a condensation of ectomesenchyme occurs in the angle formed by the division of the inferior alveolar nerve and its incisor and mental branches. At seven weeks, intramembranous ossification begins in this condensation, forming the first bone of the mandible (Figure 1.7). From this center of ossification, bone formation spreads rapidly anteriorly to the midline and posteriorly toward the point where the mandibular nerve divides into its lingual and inferior alveolar branches. This spread of new bone formation occurs anteriorly along the lateral aspect of Meckel’s cartilage, forming a trough that consists of lateral and medial plates that unite beneath the incisor nerve. This trough of bone extends to the midline, where it comes into approximation with a similar trough formed in
The further growth of the mandible until birth is influenced strongly by the appearance of three secondary cartilages and the development of muscular attachments: (1) the condylar cartilage, which is most important; (2) the coronoid cartilage; and (3) the symphyseal cartilage.

The condylar cartilage appears during the 12th week of development and rapidly forms a cone-shaped or carrot-shaped mass that occupies most of the developing ramus. This mass of cartilage is converted quickly to bone by endochondral ossification so that at 20 weeks, only a thin layer of cartilage remains in the condylar head. This remnant of cartilage persists until the end of the second decade of life, providing a mechanism for growth of the mandible in the same way as the epiphyseal cartilage does in the limbs.

The coronoid cartilage appears at about four months of development, surmounting the anterior border and top of the coronoid process. Coronoid cartilage is a transient growth cartilage and disappears long before birth. The symphyseal cartilages, two in number, appear in the connective tissue between the two ends of Meckel's cartilage but are entirely independent of it. They are obliterated within the first year after birth.

**Maxilla**

The maxilla also develops from a center of ossification in the mesenchyme of the maxillary process of the first arch. No arch cartilage or primary cartilage exists in the maxillary process, but the center of ossification is associated closely with the cartilage of the nasal capsule. As in the mandible, the center of ossification appears in the angle between the divisions of a nerve (i.e., where the anterosuperior dental nerve is given off from the inferior orbital nerve). From this center, bone formation spreads posteriorly below the orbit toward the developing zygoma and anteriorly toward the future incisor region. Ossification also spreads superiorly to form the frontal process and downward to form the lateral alveolar plate for the maxillary tooth germs. Ossification also spreads into the palatine process to form the hard palate. The medial alveolar plate develops from the junction of the palatine process and the main body of the forming maxilla. This plate, together with its lateral counterpart, forms a trough of bone around the maxillary tooth germs that eventually become enclosed in bony crypts.

A secondary cartilage also contributes to the development of the maxilla. A zygomatic, or malar, cartilage appears in the developing zygomatic process and for a short time adds considerably to the development of the maxilla. At birth, the frontal process of the maxilla is well marked, but the body of the bone consists of little more than the alveolar process containing the tooth germs and

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**Figure 1.8** Photomicrograph of a coronal section through an embryo showing the general pattern of intramembranous bone deposition associated with formation of the mandible. The relationship among nerve, cartilage, and tooth germ is evident. Arrowheads indicate the future directions of bone growth to form the neural canal and lateral and medial alveolar plates. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)