Mineralized Tissues in Oral and Craniofacial Science

Biological Principles and Clinical Correlates
Mineralized Tissues in Oral and Craniofacial Science
Biological Principles and Clinical Correlates

Edited by

Laurie K. McCauley, DDS, PhD
William K. and Mary Anne Najjar Professor and Chair
Department of Periodontics and Oral Medicine
Professor, Department of Pathology
University of Michigan
Ann Arbor, Michigan
USA

Martha J. Somerman, DDS, PhD
Former Dean and Professor, University of Washington School of Dentistry
Seattle, Washington
Director, National Institute of Dental and Craniofacial Research
Chief, Laboratory for Oral Connective Tissue Biology
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
Bethesda, Maryland
USA

WILEY-BLACKWELL
A John Wiley & Sons, Inc., Publication
## Contents

<table>
<thead>
<tr>
<th>Contributors</th>
<th>vii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>xv</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>xvii</td>
</tr>
<tr>
<td>Foreword</td>
<td>xix</td>
</tr>
</tbody>
</table>

### Section 1  Bones of the oral-dental and craniofacial complex 1

1 Embryology of craniofacial bones  
Antonio Nanci and Pierre Moffatt  
(3)

2 Clinical correlate: cleft lip and palate  
Emily R. Gallagher and Joel Berg  
(13)

3 Cell and molecular biology of the osteoclast and bone resorption  
Martin Biosse-Duplan, William C. Horne, and Roland Baron  
(17)

4 Clinical correlate: osteopetrosis  
Paul C. Edwards and Nasser Said-Al-Naief  
(29)

5 Clinical correlate: CLCN7-associated autosomal recessive osteopetrosis  
Piranit Nik Kantaputra  
(35)

6 Osteoblasts of craniofacial bone  
Renny T. Franceschi, Chunxi Ge, and Christopher G. Wilson  
(43)

7 Clinical correlate: cleidocranial dysplasia  
Shu Takeda, Nobuhiko Haga, and Keiji Moriyama  
(59)

8 Cell biology of craniofacial bone: osteocytes  
Lynda F. Bonewald  
(63)

9 Clinical correlate: Van Buchem disease  
H.-J. Prins, A.L.J.J. Bronckers, and J. Klein-Nulend  
(71)

10 Stem cell biology in the craniofacial apparatus  
Carolina Parada, Kentaro Akiyama, Yang Chai, and Songtao Shi  
(79)

11 Clinical correlate: stem cell therapy for craniofacial bone regeneration  
Giorgio Pagni, William V. Giannobile, and Darnell Kaigler  
(93)

12 Extracellular matrix and mineralization of craniofacial bone  
Marc D. McKee, Monzur Murshed, and Mari T. Kaartinen  
(99)

13 Clinical correlate: osteogenesis imperfecta  
Peter H. Byers  
(111)

### Section 2  Teeth 117

14 Tooth development  
Irma Thesleff and Emma Juuri  
(119)

15 Clinical correlate: tooth agenesis  
Rena N. D’Souza and Gabriele I. Mues  
(129)

16 Dentin  
Chunlin Qin and Jian Q. Feng  
(135)

17 Clinical correlate: dentinogenesis imperfecta, restorative procedures, and caries  
Yong-Hee Patricia Chun and Jan CC. Hu  
(143)

18 Enamel fabrication: the story of amelogenesis  
Carolyn W. Gibson and Malcolm L. Snead  
(153)
19 Clinical correlate: amelogenesis imperfecta
   Rochelle G. Lindemeyer

20 Cementum
   Brian L. Foster and Martha J. Somerman

21 Clinical correlate: case study of identical twins with cementum and periodontal defects resulting from odontohypophosphatasia

22 Dental engineering: tooth regeneration
   Weibo Zhang and Pamela C. Yelick

23 Clinical correlate: periodontal regeneration
   Jia-Hui Fu and Hom-Lay Wang

24 Clinical correlate: natural tooth regeneration
   Gary E. Heyamoto

25 Clinical correlate: regenerative endodontics in an immature tooth with pulpal necrosis and periapical pathosis
   Tatiana M. Botero, Christine M. Sedgeley, Martha I. Paniagua, and Diego M. Tobón

Section 3 Bones and teeth

26 Bone and tooth interface: periodontal ligament
   P. Mark Bartold

27 Clinical correlate: two cases of destructive periodontal disease
   Rahime Meral Nohutcu

28 Periodontal disease and inflammation-induced bone remodeling
   Dana T. Graves, Elliot D. Rosenstein, Carlos Rossa Jr., and Joseph P. Fiorellini

29 Clinical correlate: endodontic lesions
   Matthew DiAndreth and Hongjiao Ouyang

30 Biomechanics of teeth in bone: function, movement, and prosthetic rehabilitation
   Susan W. Herring

31 Clinical correlate: biomechanics of teeth in bone
   Gregory King, Geoffrey Greenlee, Paola Leone, and Gregory Vaughn

32 Impact of metabolic bone disease on craniofacial bones and teeth
   Jill Bashutski, L. Susan Taichman, and Laurie K. McCauley

33 Clinical correlate: renal osteodystrophy
   Flavia Pirih, Gabriella Tehrany, and Tara Aghaloo

34 Mineral metabolism and its impact on craniofacial bones and teeth
   Jian Q. Feng and Chunlin Qin

35 Clinical correlate: mineral metabolism and disruption of dentoalveolar development in a case of craniometaphyseal dysplasia (CMD)
   Hai Zhang and Brian Foster

36 Sun, nutrition, and the mineralization of bones and teeth
   Philippe P. Hujoel

37 Clinical correlate: vitamin D deficiency
   Ana Lucia Seminario and Elizabeth Velan

38 Impact of therapeutic modalities on craniofacial bones and teeth
   Purnima S. Kumar and Angelo Mariotti

39 Clinical correlate: osteoradionecrosis of the jaws (ORN)
   Nicholas M. Makhoul and Brent B. Ward

Index

Figures from the book are available for download at www.wiley.com/go/mccauley
Contributors

Editors
Laurie K. McCauley, DDS, PhD
William K. and Mary Anne Najjar Professor and Chair,
Department of Periodontics and Oral Medicine
Professor, Department of Pathology
University of Michigan
Ann Arbor, Michigan, USA

Martha J. Somerman, DDS, PhD
Former Dean and Professor, University of Washington
School of Dentistry
Seattle, Washington, USA
Director, National Institute of Dental and Craniofacial
Research
Chief, Laboratory for Oral Connective Tissue Biology
National Institute of Arthritis and Musculoskeletal and
Skin Diseases
National Institutes of Health
Bethesda, Maryland, USA

Roland Baron, DDS, PhD
Professor and Chair
Oral Medicine, Infection and Immunity
Harvard School of Dental Medicine
Professor
Harvard Medical School
Endocrine Unit
Massachusetts General Hospital
Boston, Massachusetts, USA

P. Mark Bartold, BDS, BScDent(Hons), PhD, DDSc,
FRACDS(Perio)
Colgate Australian Clinical Dental Research Centre
School of Dentistry
University of Adelaide
Adelaide, South Australia, Australia

Jill Bashutski, DDS, MS
Clinical Assistant Professor
Discipline Coordinator for Undergraduate Periodontics
Department of Periodontics and Oral Medicine
University of Michigan
Ann Arbor, Michigan, USA

Joel Berg, DDS, MS
Professor
Lloyd and Kay Chapman Chair for Oral Health
Director, Department of Dentistry
Seattle Children’s Hospital
Associate Dean for Hospital Affairs
Chair, Department of Pediatric Dentistry
University of Washington School of Dentistry
Seattle, Washington, USA

Martin Biosse-Duplan, DDS, PhD
Instructor, Department of Biological Sciences and
Department of Periodontics
Faculté de Chirurgie Dentaire
Université Paris
Descartes Paris, France

Contributors
Tara Aghaloo, DDS, MD, PhD
Associate Professor
Oral and Maxillofacial Surgery and Diagnostic and
Surgical Sciences
University of California, Los Angeles, School of
Dentistry
Los Angeles, California, USA

Kentaro Akiyama, DDS, PhD
Research Associate
Ostrow School of Dentistry
Center for Craniofacial Molecular Biology
University of Southern California
Los Angeles, California, USA
Department of Oral Rehabilitation and Regenerative
Medicine, Okayama University Graduate School of
Medicine, Dentistry, and Pharmaceutical Sciences,
Okayama, Japan
Lynda F. Bonewald, PhD  
Vice Chancellor for Research Interim  
Curator’s Professor  
Lee M and William Lefkowitz Professor  
Director, Bone Biology Research Program  
Director, UMKC Center of Excellence in Mineralized Tissues  
University of Missouri at Kansas City  
School of Dentistry, Department of Oral Biology  
Kansas City, Missouri, USA

Tatiana M. Botero, DDS, MS  
Clinical Associate Professor  
Cariology, Restorative Science and Endodontics  
School of Dentistry  
University of Michigan  
Ann Arbor, Michigan, USA

A.L.J.J. Bronckers, PhD  
Associate Professor  
Department of Oral Cell Biology  
ACTA-University of Amsterdam and VU University Amsterdam  
Research Institute MOVE  
Amsterdam, The Netherlands

Peter H. Byers, MD  
Professor, Departments of Pathology and Medicine (Medical Genetics)  
Adjunct Professor, Departments of Oral Biology and Genome Sciences  
University of Washington  
Seattle, Washington, USA

Yang Chai, DDS, PhD  
George and Mary Lou Boone Professor  
Director, Center for Craniofacial Molecular Biology  
Associate Dean of Research  
Ostrow School of Dentistry  
University of Southern California  
Los Angeles, California, USA

Yong-Hee Patricia Chun, DDS, MS, PhD  
Assistant Professor/Research  
Department of Periodontics  
School of Dentistry  
University of Texas Health Science Center at San Antonio  
San Antonio, Texas, USA

Matthew DiAndreth, DMD, MS  
Private Practice  
Pittsburgh, Pennsylvania, USA

Rena N. D’Souza, DDS, PhD  
Professor and Chair  
Department of Biomedical Sciences  
Texas A&M Health Science Center  
Baylor College of Dentistry  
Dallas, Texas, USA

Paul C. Edwards, MSc, DDS, FRCD(C)  
Associate Professor (Clinical), Department of Periodontics and Oral Medicine  
Division of Oral Pathology, Medicine and Radiology  
University of Michigan School of Dentistry  
Ann Arbor, Michigan, USA

Jian Q. Feng, MD, PhD  
Professor  
Biomedical Sciences  
Baylor College of Dentistry  
Texas A&M Health Science Center  
Dallas, Texas, USA

Joseph P. Fiorellini, DMD, DMSc  
Professor and Chair of Periodontics  
University of Pennsylvania  
School of Dental Medicine  
Department of Periodontics  
Philadelphia, Pennsylvania, USA

Brian L. Foster, PhD  
Research Fellow  
Laboratory for Oral Connective Tissue Biology  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
National Institutes of Health  
Bethesda, Maryland, USA

Renny T. Franceschi, PhD  
Professor of Dentistry, Biological Chemistry and Biomedical Engineering  
Department of Periodontics and Oral Medicine  
University of Michigan School of Dentistry  
Ann Arbor, Michigan, USA

Jia-Hui Fu, BDS, MS  
Assistant Professor  
Department of Periodontics  
National University of Singapore  
Singapore
Emily R. Gallagher, MD, MPH
Assistant Professor, Department of Pediatrics
Medical Director, Craniofacial Disorders Program
Oregon Health and Sciences University
Portland, Oregon, USA

Chunxi Ge, MD, PhD
Research Investigator
Department of Periodontics and Oral Medicine
University of Michigan School of Dentistry
Ann Arbor, Michigan, USA

Ana Paula Georgetti, DDS, MS
PhD Student, Department of Prosthodontics and Periodontics
Division of Periodontics
School of Dentistry at Piracicaba
State University of Campinas
Piracicaba, São Paulo, Brazil

William V. Giannobile, DDS, DMSc
Najjar Endowed Professor of Dentistry, Department of Periodontics and Oral Medicine, School of Dentistry
Professor, Department of Biomedical Engineering, College of Engineering
Director, Michigan Center for Oral Health Research
University of Michigan
Ann Arbor, Michigan, USA

Carolyn W. Gibson, PhD
Professor
Department of Anatomy and Cell Biology
University of Pennsylvania School of Dental Medicine
Philadelphia, Pennsylvania, USA

Dana T. Graves, DDS, DMSc
Professor and Associate Dean for Translational Research
Department of Periodontics
University of Pennsylvania School of Dental Medicine
Philadelphia, Pennsylvania, USA

Geoffrey Greenlee, DDS, MSD, MPH
Clinical Assistant Professor
Department of Orthodontics
University of Washington
Seattle, Washington, USA

Nobuhiko Haga, MD, PhD
Professor
Department of Rehabilitation Medicine
Graduate School of Medicine
The University of Tokyo
Tokyo, Japan

Susan W. Herring, PhD
Department of Orthodontics
University of Washington
Seattle, Washington, USA

Gary E. Heyamoto, DDS
Private Practice
Bothell, Washington, USA

William C. Horne, PhD
Lecturer
Oral Medicine, Infection and Immunity
Harvard School of Dental Medicine
Boston, Massachusetts, USA

Jan CC. Hu, BDS, PhD
Professor
Biologic and Materials Sciences
School of Dentistry
University of Michigan
Ann Arbor, Michigan, USA

Philippe P. Hujoel, PhD, MSD, DDS, MS
Professor, Oral Health Sciences
Adjunct Professor, Epidemiology
Department of Dental Public Health Sciences
School of Dentistry
University of Washington
Seattle, Washington, USA

Emma Juuri, MSc, DDS
PhD Student
Developmental Biology Program
Institute of Biotechnology
University of Helsinki
Helsinki, Finland

Mari T. Kaartinen, PhD
Associate Professor
Faculty of Dentistry
Faculty of Medicine
McGill University
Montréal, Québec, Canada
Contributors

Darnell Kaigler, DDS, MS, PhD
Department of Periodontics and Oral Medicine
Michigan Center for Oral Health Research
Department of Biomedical Engineering
University of Michigan
Ann Arbor, Michigan, USA

Piranit Nik Kantaputra, DDS, MS
Division of Pediatric Dentistry
Department of Orthodontics and Pediatric Dentistry
Craniofacial Genetics Laboratory
Faculty of Dentistry
Chiang Mai University
Chiang Mai, Thailand

Gregory King, DMD, DMSc
Professor
Department of Orthodontics
University of Washington
School of Dentistry
Seattle, Washington, USA

J. Klein-Nulend, PhD
Professor
Department of Oral Cell biology
ACTA-University of Amsterdam and VU University
Amsterdam
Research Institute MOVE
Amsterdam, The Netherlands

Purnima S. Kumar, PhD
Assistant Professor
Department of Periodontology
The Ohio State University
Columbus, Ohio, USA

Paola Leone, DDS, MSD
Affiliate Associate Professor
Department of Orthodontics
University of Washington
School of Dentistry
Seattle, Washington, USA

Rochelle G. Lindemeyer, DMD
Associate Professor
Division of Pediatric Dentistry
University of Pennsylvania School of Dental Medicine
Philadelphia, Pennsylvania, USA

Nicholas M. Makhoul, DMD, MD
Fellow, Maxillofacial Oncology and Microvascular Reconstructive Surgery
Section Oral and Maxillofacial Surgery
Department of Surgery
University of Michigan
Ann Arbor, Michigan, USA

Angelo Mariotti, DDS, PhD
Professor and Chair
Division of Periodontology
The Ohio State University
Columbus, Ohio, USA

Luciane Martins, BS, MS, PhD
Post-Doctoral, Department of Prosthodontics and Periodontics, Division of Periodontics
School of Dentistry at Piracicaba
State University of Campinas
Piracicaba, Sao Paulo, Brazil

Marc D. McKee, PhD
James McGill Professor
Division of Biomedical Sciences
Faculty of Dentistry
Department of Anatomy and Cell Biology
Faculty of Medicine
McGill University
Montréal, Québec, Canada

Pierre Moffatt, PhD
Assistant Professor
Shriners Hospital for Children
Department of Human Genetics
McGill University
Montréal, Québec, Canada

Keiji Moriyama, DDS, PhD
Professor and Chairman
Department of Maxillofacial Orthognathics
Tokyo Medical Hospital and Dental University
Graduate School
Tokyo, Japan

Gabriele I. Mues, MD, PhD
Assistant Professor
Department of Biomedical Sciences
TAMHSC Baylor College of Dentistry
Dallas, Texas, USA
Monzur Murshed, PhD
Assistant Professor
Department of Medicine and Faculty of Dentistry
McGill University
Montréal, Québec, Canada

Antonio Nanci, PhD
Professor
Department of Stomatology
Faculty of Dentistry
Université de Montréal
Montréal, Québec, Canada

João S. Pereira Neto, DDS, MS, PhD
Assistant Professor, Department of Pediatric Dentistry
Division of Orthodontics
School of Dentistry at Piracicaba
State University of Campinas
Piracicaba, São Paulo, Brazil

Francisco H. Nociti Jr.
Professor, Department of Prosthodontics and Periodontics, Division of Periodontics
School of Dentistry at Piracicaba
State University of Campinas
Piracicaba, Sao Paulo, Brazil
Senior Scientist, Visiting Program
National Institute of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS)
Bethesda, Maryland, USA

Rahime Meral Nohutcu, DDS, PhD
Professor
Department of Periodontology
Faculty of Dentistry
Hacettepe University
Ankara, Turkey

Hongjiao Ouyang, DMD, PhD
Assistant Professor
Department of Medicine
Department of Microbiology and Molecular Genetics
The Center for Bone Biology at University of Pittsburgh Medical Center
The Center for Multiple Myeloma at University of Pittsburgh Medical Center School of Medicine
Department of Comprehensive Care, Restorative Dentistry and Endodontics
School of Dental Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Giorgio Pagni, DDS, MS
Department of Periodontics and Oral Medicine
Michigan Center for Oral Health Research
University of Michigan
Ann Arbor, Michigan, USA
Private Practice
Florence, Italy

Martha I. Paniagua, DDS
Assistant Professor
Department Endodontics
School of Dentistry
University CES
Medellín, Colombia

Carolina Parada, DDS, PhD
Research Associate
Center for Craniofacial Molecular Biology
Ostrow School of Dentistry
University of Southern California
Los Angeles, California, USA

Flavia Pirih, DDS, PhD
Adjunct Assistant Professor
Department of Periodontics
University of California, Los Angeles, School of Dentistry
Los Angeles, California, USA

H.-J. Prins, PhD
Postdoctoral Research Fellow
Department of Oral Cell Biology
ACTA-University of Amsterdam and VU University Amsterdam
Research Institute MOVE
Amsterdam, The Netherlands

Chunlin Qin, DDS, PhD
Associate Professor
Department of Biomedical Sciences, Baylor College of Dentistry
Texas A&M Health Science Center
Dallas, Texas, USA

Thaisângela L. Rodrigues, DDS, MS, PhD
Fellow, Department of Prosthodontics and Periodontics
Division of Periodontics
School of Dentistry at Piracicaba
State University of Campinas
Piracicaba, São Paulo, Brazil
Elliot D. Rosenstein, MD
Associate Clinical Professor, Division of Clinical Immunology
Mount Sinai School of Medicine
New York, New York, USA
Director, Institute of Rheumatic and Autoimmune Diseases
Overlook Medical Center
Summit, NJ, USA

Carlos Rossa Jr., DDS, PhD
Associate Professor
Department of Diagnosis and Surgery
School of Dentistry at Araraquara-State University of São Paulo (UNESP)
Araraquara, São Paulo, Brazil

Nasser Said-Al-Naief, DDS, MS
Associate Professor of Pathology and Medicine
Director, Oral and Maxillofacial Pathology Laboratory
Director, Clinical Oral Pathology/Oral Medicine
University of the Pacific
San Francisco, California, USA

Christine M. Sedgley, MDS, MDSc, FRACDS, MRACDS(ENDO), PhD
Associate Professor and Chair
Department of Endodontology
School of Dentistry
Oregon Health and Science University
Portland, Oregon, USA

Ana Lucia Seminario, DDS, PhD
Acting Assistant Professor
Department of Pediatric Dentistry
University of Washington
Seattle, Washington, USA

Songtao Shi, DDS, PhD
Associate Professor
Herman Ostrow School of Dentistry
University of Southern California
Los Angeles, California, USA

Malcolm L. Snead, DDS, PhD
Professor
Center for Craniofacial Molecular Biology
Los Angeles, California, USA

L. Susan Taichman, RDH, MPH, PhD
Assistant Professor/Research Scientist
Department of Periodontics and Oral Medicine
University of Michigan School of Dentistry
Ann Arbor, Michigan, USA

Gabriella Tehrany, DDS, MD
Associate Surgeon, Maxillofacial Surgery
Kaiser Permanente
Lecturer, University of California, Los Angeles, Oral and Maxillofacial Surgery
Los Angeles, California, USA

Shu Takeda, MD, PhD
Junior Research Associate Professor
Center of Excellence Program for Frontier Research on Molecular Destruction and Reconstruction of Tooth and Bone
Department of Orthopedic Surgery
Tokyo Medical and Dental University
Tokyo, Japan

Irma Thesleff, DDS, PhD
Professor, Research Director
Developmental Biology Program
Institute of Biotechnology
University of Helsinki
Helsinki, Finland

Diego M. Tobón, DDS
Professor
Director of Endodontics
School of Dentistry
University CES
Medellín, Colombia

Gregory Vaughn, DDS
Affiliate Associate Professor
Department of Orthodontics
University of Washington
School of Dentistry
Seattle, Washington, USA

Elizabeth Velan, DMD MSD
Seattle Children’s Hospital
Seattle, Washington, USA

Hom-Lay Wang, DDS, MS, PhD
Professor, School of Dentistry
Collegiate Professor of Periodontology
Director, Graduate Periodontics
University of Michigan
Ann Arbor, Michigan, USA
Brent B. Ward, DDS, MD, FACS
Assistant Professor and Fellowship Program Director
Maxillofacial Oncology and Reconstructive Surgery
Oral and Maxillofacial Surgery
University of Michigan
Ann Arbor, Michigan, USA

Christopher G. Wilson, PhD
Research Fellow
Department of Periodontics and Oral Medicine
University of Michigan School of Dentistry
Ann Arbor, Michigan, USA

Pamela C. Yelick, PhD
Professor and Director, Division of Craniofacial and Molecular Genetics
Department of Oral and Maxillofacial Pathology
Tufts University
Boston, Massachusetts, USA

Hai Zhang, DMD, PhD
Associate Professor
Department of Restorative Dentistry
School of Dentistry
University of Washington
Seattle, Washington, USA

Weibo Zhang, MDS, PhD
Research Associate, Division of Craniofacial and Molecular Genetics
Department of Oral and Maxillofacial Pathology
Tufts University
School of Dental Medicine
Boston, Massachusetts, USA
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 nondental 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
Martha J. Somerman
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.
M.J.S.
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.

Philip Stashenko, DMD, PhD
Chief Executive Officer
The Forsyth Institute

Thomas Van Dyke, DDS, MS, PhD
Vice President of Clinical and Translational Research
The Forsyth Institute
SECTION 1
Bones of the oral-dental and craniofacial complex
Embryology of craniofacial bones

Antonio Nanci and Pierre Moffatt

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).

The primitive oral cavity is at first bounded above (rostrally) by the frontal prominence, below (caudally) by the developing heart, and laterally by the first branchial arch. With the midventral expansion of arches, the cardiac plate is pushed away, and the floor of the mouth is formed by the first, second, and third branchial arches.

At about 28 first arch because it forms in front of the buccopharyngeal membrane). The central core consists of mesenchyme derived from lateral plate mesoderm that is invaded by NCCs. The resulting ectomesenchyme condenses to form a bar of cartilage, the arch cartilage. The cartilage of the first arch is called Meckel’s cartilage, and that of the second is Reichert’s cartilage; the remaining arch cartilages are not named.

The primitive oral cavity is at first bounded above (rostrally) by the frontal prominence, below (caudally) by the developing heart, and laterally by the first branchial arch. With the midventral expansion of arches, the cardiac plate is pushed away, and the floor of the mouth is formed by the first, second, and third branchial arches.

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

---

**Figure 1.2** Migrating neural crest cells (NCCs) express the same homeobox (Hox) genes as their precursors in the rhombomeres from which they derive. Note that Hox genes are not expressed anterior to rhombomere 3. A new set of patterning genes (Msx, Dlx, and Barx) has evolved to bring about the development of cephalic structures so that a “Hox code” also is transferred to the branchial arches and developing face. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

**Figure 1.3** A 27-day embryo viewed from the front. The beginning elements for facial development and the boundaries of the stomatodeum are apparent. The first arch gives rise to maxillary and mandibular processes. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)
Bones of the oral-dental and craniofacial complex

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.
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...
Bones of the oral-dental and craniofacial complex

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

the adjoining mandibular process (Figure 1.8). The two separate centers of ossification remain separated at the mandibular symphysis until shortly after birth.

Similarly, a backward extension of ossification along the lateral aspect of Meckel’s cartilage forms a gutter that is later converted into a canal that contains the inferior alveolar nerve. This backward extension of ossification proceeds in the condensed mesenchyme to the point where the mandibular nerve divides into the inferior alveolar and lingual nerves. From this bony canal, medial and lateral alveolar plates of bone develop in relation to the forming tooth germs so that the tooth germs occupy a secondary trough of bone. This trough is partitioned, and thus the teeth come to occupy individual compartments that are finally enclosed totally by growth of bone over the tooth germ (Figure 1.8). The ramus of the mandible develops by a rapid spread of ossification posteriorly into the mesenchyme of the first arch, turning away from Meckel’s cartilage. Thus, by 10 weeks the rudimentary mandible is formed almost entirely by membranous ossification, with no apparent involvement of Meckel’s cartilage.

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.)