Cover image illustrating the innervation of normal human dental pulp using antibodies for neurons (N52, green; PGP, blue) and the receptor TRPA1 (red). Image courtesy of Michael A. Henry, DDS, PhD.
# Table of Contents

Preface vii
Contributors viii

1 Development of the Pulpodentin Complex 1
   Rena D’Souza and Chunlin Qin

2 Formation and Repair of Dentin in the Adult 27
   Anthony J. Smith

3 Pulpodentin Complex 47
   David H. Pashley and Franklin R. Tay

4 Pulp as a Connective Tissue 67
   Takashi Okiji

5 Stem Cells and Regeneration of the Pulpodentin Complex 91
   Peter E. Murray and Franklin García-Godoy

6 Circulation of the Pulp 109
   Hideharu Ikeda and Hideaki Suda

7 Dental Innervation and Its Responses to Tooth Injury 133
   Margaret R. Byers, Michael A. Henry, and Matti V. O. Närhi

8 Pain Pathways and Mechanisms of the Pulpodentin Complex 159
   Anibal Diogenes and Michael A. Henry

9 Pharmacologic Control of Dental Pain 185
   Asma Khan and Kenneth M. Hargreaves

10 Pulpal Infections, Including Caries 205
   José F. Siqueira, Jr

11 Molecular Mediators of Pulpal Inflammation 241
   Ashraf F. Fouad

12 Interrelationship of the Pulp and Apical Periodontitis 277
   Hajime Sasaki and Philip Stashenko
13 Repair of Pulpal Injury with Dental Materials 301

14 Caries, Restorative Dentistry, and the Pulp 323
Franklin R. Tay, Harold Messer, and Richard Schwartz

15 Effects of Thermal and Mechanical Challenges 349
Harold E. Goodis and David H. Pashley

16 Interrelationship of Pulpal and Periodontal Diseases 373
Ilan Rotstein and James H. Simon

17 Root Resorption 397
Linda G. Levin

18 Aging and the Pulp 421
Harold E. Goodis, Arnold Kahn, and Stéphane Simon

19 Differential Diagnosis of Toothache: Odontogenic Versus Nonodontogenic Pain 447
Jeffrey P. Okeson

20 Interrelationship of Pulp and Systemic Disease 471
Michaell A. Huber

Index 493
Preface

Welcome to the second edition of Seltzer and Bender’s Dental Pulp. Like the first edition, this book focuses on the dental pulp and its interaction with other tissues during health and disease, with each chapter providing the latest information on the biological principles and the basis for clinical treatment procedures. As such, the book is ideally suited for practicing dentists as well as residents and dental students. This newly revised second edition includes entirely new topics (eg, regenerative endodontics) as well as greatly expanded reviews on dental implications of biofilms, immune interactions, pain mechanisms, the interactions between restorative dental procedures and pulpal health, and neuroanatomy, among other topics. We welcome many new and returning authors to this edition who have shared their incredible expertise with you, our reader.

The central theme of this book—a fundamental theme of dentistry in our opinion—is the critical role that pulp tissue plays in dental health. Both local (eg, caries, periodontitis) and systemic (eg, referred pain) conditions. The astute clinician needs this information to provide accurate diagnoses and effective treatment. Accordingly, we have focused on the biology of dental pulp and its interaction with other tissues during health and disease in order to provide comprehensive, biologically based clinical recommendations for practicing dentists.

We have been gratified by the support and encouragement generated from the first edition of this text, and we were thrilled that both I. B. Bender and Sam Seltzer lived to enjoy its publication. We have now lost many of the pioneering giants of endodontics and pulp biology. Their early contributions laid the foundation for generations of dentists to deliver biologically based dental care. In this age of gene arrays, signal transduction pathways, novel restorative materials, and computerized data retrieval, it is difficult to appreciate the magnitude of their contributions based entirely upon intellectual rigor and using relatively simple tools. To their memories, we dedicate this second edition.
Contributors

Margaret R. Byers, PhD
Professor Emeritus
Department of Anesthesiology and Pain Medicine
University of Washington
Seattle, Washington

Anibal Diogenes, DDS, MS, PhD
Assistant Professor
Department of Endodontics
University of Texas Health Science Center at San Antonio
San Antonio, Texas

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

Ashraf F. Fouad, BDS, DDS, MS
Professor and Chair
Department of Endodontics, Prosthodontics, and Operative Dentistry
Director
Postgraduate Endodontics
University of Maryland Dental School
Baltimore, Maryland

Franklin García-Godoy, DDS, MS
Professor and Senior Executive Associate Dean of Research
University of Tennessee Health Science Center
Memphis, Tennessee

Harold E. Goodis, DDS
Professor Emeritus
Department of Preventive and Restorative Dental Sciences
University of California at San Francisco
San Francisco, California

Kenneth M. Hargreaves, DDS, PhD
Professor and Chair
Department of Endodontics
Professor
Departments of Pharmacology, Physiology, and Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Michael A. Henry, DDS, PhD
Professor
Department of Endodontics
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Michaell A. Huber, DDS
Associate Professor
Oral Medicine Subject Expert
Department of Comprehensive Dentistry
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Hideharu Ikeda, DDS, PhD
Associate Professor
Department of Pulp Biology and Endodontics
Graduate School of Medical and Dental Sciences
Tokyo Medical and Dental University
Tokyo, Japan

Arnold Kahn, PhD
Senior Scientist
California Pacific Medical Center Research Institute
Professor Emeritus and Former Chair
Department of Cell and Tissue Biology
School of Dentistry
University of California at San Francisco
San Francisco, California

Asma Khan, BDS, PhD
Assistant Professor
Department of Endodontics
University of North Carolina
Chapel Hill, North Carolina
Linda G. Levin, DDS, PhD
Former Chair
Department of Endodontics
University of North Carolina
Chapel Hill, North Carolina
Private practice
Durham, North Carolina

Sally Marshall, PhD
Professor
Division of Biomaterials and Bioengineering
Department of Preventive and Restorative Dental Sciences
University of California at San Francisco
San Francisco, California

Grayson W. Marshall, Jr, DDS, MPH, PhD
Professor and Chair
Division of Biomaterials and Bioengineering
Department of Preventive and Restorative Dental Sciences
University of California at San Francisco
San Francisco, California

Harold Messer, MDSc, PhD
Professor Emeritus
Melbourne Dental School
The University of Melbourne
Melbourne, Australia

Peter E. Murray, BSc (Hons), PhD
Professor
Department of Endodontics
College of Dental Medicine
Nova Southeastern University
Fort Lauderdale, Florida

Matti V. O. Närhi, DDS, PhD
Professor, Chair, and Research Director
Department of Physiology
Institute of Biomedicine
University of Eastern Finland
Kuopio, Finland

Jeffrey P. Okeson, DMD
Professor and Chair
Department of Oral Health Science
Director
Orofacial Pain Program
College of Dentistry
University of Kentucky
Lexington, Kentucky

Takashi Okiji, DDS, PhD
Professor
Division of Cariology, Operative Dentistry, and Endodontics
Department of Oral Health Sciences
Graduate School of Medical and Dental Sciences
Niigata University
Niigata, Japan

David H. Pashley, DMD, PhD
Emeritus Regents’ Professor
Department of Oral Biology
College of Dental Medicine
Georgia Health Sciences University
Augusta, Georgia

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

Ilan Rotstein, DDS
Professor and Chair
Division of Endodontics, Oral and Maxillofacial Surgery, and Orthodontics
University of Southern California
Los Angeles, California

Hajime Sasaki, DDS, PhD
Assistant Member of the Staff
Department of Cytokine Biology
The Forsyth Institute
Cambridge, Massachusetts
Richard Schwartz, DDS
Clinical Assistant Professor
Department of Endodontics
University of Texas Health Science Center at San Antonio
San Antonio, Texas

James H. Simon, DDS
Director
Advanced Endodontic Program
Wayne G. and Margaret L. Bemis Endowed Professor
Division of Endodontics, Oral and Maxillofacial Surgery, and Orthodontics
University of Southern California
Los Angeles, California

Stéphane Simon, DDS, MPhil, PhD
Senior Lecturer
Department of Endodontics
University of Paris 7, Diderot
Paris, France

José F. Siqueira, Jr, DDS, MSc, PhD
Professor and Chair
Department of Endodontics
Faculty of Dentistry
Estácio de Sá University
Rio de Janeiro, Brazil

Anthony J. Smith, BSc, PhD
Professor
Department of Oral Biology
School of Dentistry
University of Birmingham
Birmingham, United Kingdom

Philip Stashenko, DMD, PhD
President and CEO
The Forsyth Institute
Cambridge, Massachusetts
Associate Professor
Department of Oral Medicine, Infection, and Immunity
Harvard University
Cambridge, Massachusetts

Hideaki Suda, DDS, PhD
Professor
Department of Pulp Biology and Endodontics
Graduate School of Medical and Dental Sciences
Tokyo Medical and Dental University
Tokyo, Japan

Franklin R. Tay, BDSc (Hons), PhD
Associate Professor
Departments of Endodontics and Oral Biology
Georgia Health Sciences University
Augusta, Georgia
Advances in living standards, including medical and dental care, have contributed to increased life spans and a growing proportion of elderly people in the population. The elderly often need more medical and dental services compared to the average citizen, including root canal treatment. Results of a survey of Diplomates of the American Board of Endodontists indicated that Diplomates examine patients covering a wide spectrum of ages but most fall into the age range of 45 to 64 years. Respondents indicated that about 26% of their patients are at least 65 years old. A substantial majority (59%) of respondents (n = 334) indicated that the number of patients aged 65 years or older is increasing in their practices.

The increased need for endodontic treatment among older individuals is due partly to naturally occurring anatomical and physiologic senescent changes that are associated with the aging process and partly to diseases that occur more commonly in older adults (see chapter 20). Oral health is important because oral diseases affect more than the mouth. Normal aging processes in healthy individuals often have few adverse effects in the oral cavity, but tooth loss, caries, periodontal diseases, and pulpal and periradicular diseases will have deleterious consequences.

The increased need for dental services for older individuals is also a reflection of the greater retention of teeth into old age. Utilization of dental care services increases with increasing age; clinical findings suggest that individuals 65 years old or older have more caries than young children, although the caries attacks cervical rather than occlusal surfaces. Further, the number of teeth with carious or restored root surfaces increases the longer a person lives; more than half the retained teeth in individuals 75 years of age or older are affected. The changes occurring in the dental pulp of elderly patients may explain the increase in requests for endodontic treatment. This chapter reviews age-dependent and age-independent processes in the dental pulp and evaluates their impact on the quality of oral health care in the elderly patient.

### Process of Aging

A discussion of aging in a particular tissue or area of the body is based on biologic theories of replicative senescence, together with the roles of oxidative stress and telomeres on the aging process. Organismal senescence is the aging of whole organisms. The term aging has commonly been equated with senescence such that the terms can be used interchangeably. The role of telomeres, structures found at the ends of chromosomes in the cells of...
Distant plasticity in the trigeminal nerve, ganglion, and central endings

The discussion so far has focused on dental sensory reactions in the terminal branches within the tooth or nearby tissues. These neurons also have extensive changes in their alveolar branches (see Fig 7-9), at their cell bodies and satellite cells in the trigeminal ganglion (see Fig 7-7), at their sensory endings in the brainstem, and in the neurons within the central nervous system. Many of the responses at the ganglion are similar to those shown for spinal nerves responding to tissue inflammation, including altered expression of neurotrophin receptors, neuropeptides, and voltage-gated ion channels by the neurons and increased expression of injury proteins by the satellite cells. Those changes can have profound
Structural and Cytochemical Responses to Tooth Injury and Infection

Effects on central pain pathways. For example, tooth injuries can cause persistent expression of the c-Fos transcription factor by central neurons, which may indicate altered central pain pathway functions. Atypical chronic dental pain and referred pain both involve long-term shifts in central processing of peripheral inputs. Chapters 8 and 9 provide further discussion of tooth pain and the extraordinary functional and cytochemical plasticity of peripheral and central neurons responding to the input of orofacial sensory neurons.

Delayed neural reactions

Both the sensory and the sympathetic fibers can have important reactions that are not launched until days or weeks after tooth injury. For example, the alveolar nerves that carry dental axons can greatly change their neuropeptide content by several weeks after a pulpal exposure in rats (see Figs 7-9d and 7-9e). The sympathetic innervation initially was not found to sprout during the early stages of neuro-pulpal reactions to pulpal exposure, but, by several weeks later, it too has focal responses directed toward the lesion. The late sympathetic reactions have a major effect on immune cell invasion of the injured pulp and may even alter the quality of tooth pain. Thus, while the initial sensory sprouting reactions are important, subsequent reactions in those fibers, in the sympathetic neurons, and at central neural pathways must also be appreciated for their roles in tooth pain.

Human teeth

The results of studies performed in animals have provided important information regarding the neuroanatomical responses in the diseased or damaged dental pulp. Certainly the advantage of these studies is that responses can be evaluated at different time points following a standardized insult. Another distinct advantage is the ability to evaluate the broad effect of these injuries within the entire trigeminal neuroaxis. Even given these advantages, some limitations exist in animal studies, and most notable is the relationship of these neuroanatomical responses to pain and especially pain in humans. In this regard, knowledge gained in animal studies must be applied to the study of the human dental pulp, where pain levels and response to stimuli can be documented prior to extraction.

The human dental pulp is richly innervated—a common source of pain—and so its use is well-suited for such studies. Also, the routine extraction of both normal third molars and diseased teeth provides an abundant supply of specimens for study. Together, the results from human and basic animal studies can further the understanding of possible correlations between neuroanatomical responses and pain mechanisms in an attempt to more fully understand pulpal pain and its important relationship to the practice of endodontics. In general, the innervation of human dental pulp (Fig 7-10) is similar to that seen in experimental animals, and these similarities strengthen the use of animals as a model for understanding response to injury in the human dental pulp.
fying processes are active at the time of the clinical evaluation and may add to the challenges associated with the diagnostic task. This chapter reviews those peripheral and central pain mechanisms that should be considered when the clinician evaluates the symptomatic patient.

Pathways Responsible for Detection, Processing, and Perception of Dental Pain

Odontogenic pain is usually the result of a noxious physical stimulus or the release of inflammatory mediators that stimulate receptors located on the terminal endings of nociceptive (pain-detecting) afferent C and Aδ nerve fibers12–16 (see chapter 7). Physical stimuli, via their effect on dentinal fluid flow, can activate the nociceptors that innervate dentinal tubules, leading to the perception of dentinal pain16 (Fig 8-2). Inflammatory mediators, via activation of their respective receptors, can sensititize or depolarize the nociceptors that innervate pulp tissue. These topics are discussed in detail later in the chapter and elsewhere.17 Experimental studies have shown that activation of nerves within the dental pulp by these physiologic (eg, thermal, mechanical, or chemical) stimuli results in a pure sensation of pain, although other studies using certain electrical stimuli can elicit a “prepain” sensation.18

The activation of the peripheral nociceptor produces a generator potential; if great enough, this depolarization will trigger a nerve impulse (action potential). The action potential is propagated along a peripheral trigeminal nerve to the primary afferent neuronal cell body located in the trigeminal ganglion and then into the central nervous system along the central process of this same neuron14,19–21 (Fig 8-3). The central process of the primary afferent cell body enters the brainstem at the level of the pons by way of the trigeminal root entry zone and then enters the trigeminal tract. The trigeminal tract carries the primary afferent fiber to the trigeminal sensory nucleus located in the pons and medulla, where it then terminates. The most rostral portion of the trigeminal sensory nucleus is the main sensory nucleus, while the caudal portion is represented by...
Pathways Responsible for Detection, Processing, and Perception of Dental Pain

**Fig 8-2** Two mechanisms for the peripheral stimulation of nociceptive nerve fibers in tooth pulp. *Acute dentinal pain:* According to the hydrodynamic theory, stimuli that cause fluid movement in exposed dentinal tubules result in the stimulation of nociceptive nerve fibers. *Pain with inflammation:* Inflammation is associated with the synthesis or release of mediators, including prostaglandins, bradykinin, substance P, and histamine (as well as other mediators not shown). The interrelationships of these inflammatory mediators form a positive feedback loop, allowing inflammation to persist far beyond cessation of the dental procedure. **P:** intrapulpal pressure; **NGI:** neurogenic inflammation; **CGRP:** calcitonin gene–related peptide; **NGF:** nerve growth factor; **GDNF:** glial cell line–derived neurotrophic factor; **NPY:** neuropeptide Y; **NE:** norepinephrine.

**Fig 8-3** Pathway and confocal micrographs of neuroanatomical structures responsible for the transmission of pulpal nociceptive stimuli within the trigeminal system. Peripheral nociceptive nerve fibers terminate as free nerve endings within the dental pulp (a) and arise from primary afferent cell bodies within the trigeminal ganglion (b). The central processes of these primary afferent cell bodies pass into the brainstem and enter the trigeminal tract. These fibers exit the tract to terminate within the trigeminal sensory nucleus (c), composed of the main sensory nucleus (MSN) and the spinal trigeminal nucleus. The trigeminal nucleus consists of pars oralis (PO), pars interpolaris (PI), and pars caudalis (PC). (a) Pulpal nerve fibers are seen within the pulp horn of a human specimen and are stained with antibodies against N52 (green), PGP9.5 (blue), and TRPA1 (red). A nerve fiber bundle (arrowhead) gives rise to an extensive arbor within the subodontoblastic plexus and with some fibers that enter and traverse (arrow) the odontoblastic layer (O). (b) Neuronal cell bodies are seen within the rat trigeminal ganglion and are stained with antibodies against peripherin (green; black arrow), TRPV1 (blue; arrowhead) and CGRP (red; white arrow). Larger cell bodies lack staining, while the smaller cell bodies are stained individually or multiply with these antibodies used to identify nociceptors. (c) Intrinsic neuronal cell bodies are stained with NeuN (green; arrow), and the central processes of CGRP-containing primary afferent fibers (red) are seen within a transverse section of the rat brainstem at the level of caudalis. The CGRP-containing primary afferent fibers are located in the trigeminal tract (T). Some of these fibers exit the tract (arrowhead) to enter and terminate especially within the superficial laminae I and II outer (a) zones of caudalis, where they form synapses with processes of intrinsic and descending neurons.

the spinal trigeminal nucleus. The spinal trigeminal nucleus is further subdivided into the following subnuclei: pars oralis (most rostral), pars interpolaris, and pars caudalis (most caudal).**22,23**

Animal studies have shown that primary afferent neurons that innervate dental pulp terminate in all of the different subnuclei located within the ipsilateral trigeminal sensory nucleus, including prominent projections to caudalis.**24** The projection to cau-
Fig 14-8  (a) Mandibular third molar of a 23-year-old woman. The radiograph does not show a caries lesion, but the tooth was extracted after repeated episodes of pericoronitis. (b) Fissure discoloration is present on the occlusal surface. The tooth was processed for light microscopy. Sections were cut on a mesiodistal plane. (c) Overview of the pulp chamber and the entire dentin thickness (hematoxylin-eosin [H&E] stain; original magnification ×25). (d and e) Progressive magnifications of the region indicated by the arrow in (c). Moderate accumulation of chronic inflammatory cells in a localized area of the subodontoblastic space (H&E stain; original magnification ×100 and ×400, respectively). (f) Disruption of the odontoblastic layer in that region (H&E stain; original magnification ×1,000). (g) Normal odontoblastic layer at a very short distance from the affected region (H&E stain; original magnification ×1,000). (Modified from Ricucci54 with permission.)

Fig 14-9  (a) Occlusal caries is present in this mandibular third molar. The pulp responded normally to sensitivity tests. The tooth was extracted. (b) Occlusal view of the extracted tooth. (c) The extent of dentinal caries became evident after a surface of the tooth was ground. (d) Despite caries penetration to the midcoronal dentin, most of the sections of the pulp exhibited normal histology. A pulp stone could be identified in the distal part of the pulp chamber (H&E stain; original magnification ×25). (e) Magnification of the rectangular area in (d). Sparse accumulation of lymphocytes (H&E stain; original magnification ×400). (f to h) Dentinal tubules directly beneath the caries lesion were colonized by bacteria (Taylor’s modified Brown & Brenn stain; original magnification ×100, ×1,000, and ×1,000, respectively). (Modified from Ricucci54 with permission.)
Responses of the Pulpodentin Complex to Caries

Inflammations may become acute and uncontrolled as bacteria approach and penetrate the pulp (Fig 14-11).

Although inflammation may be regarded as a defense response to injury, severe reactions can result initially as localized microabscesses. Further ingress of bacteria into the pulp produces clinically identifiable abscesses (Fig 14-12) that eventually result in pulpal necrosis and development of periradicular lesions (Fig 14-13). The end result of adaptive immunity is an exaggerated inflammatory response intended to eliminate the infection. However, if the source of caries infection is not eliminated, immune inflammation in pulpitis eventually leads to irreversible destruction of the pulp.

Repair responses

The pulpodentin complex reacts to stimuli from the bacterial biofilm with dentinal sclerosis and tertiary dentin formation. Dentinal sclerosis has been discussed in previous sections. Unlike primary and secondary dentinogenesis, tertiary dentinogenesis is restricted to the vicinity of the dentin that is directly affected by the caries process. It is not unusual to see partial obliteration of the dental pulp by tertiary dentin in slowly progressing caries lesions that have not undergone restorative treatment.

Tertiary dentinogenesis has been redefined in relation to the nature of the injury (see chapter 2). The term reactionary dentinogenesis has been
Glia, 165
German measles, 473–474
Genetic and developmental disorders
Gap junctions, 76, 136f
G proteins, 145
Fusobacterium species, 217
Free radicals, 423–424
FOXP3+CD25+ cells, 280
Foreign bodies, 380, 380f–381f
Fluoride
Fluorescent antibody cell sorting, 96
Fibronectin-binding protein, 333
Fibronectin, 73f, 73–74
Fibrodentin, 39
Fibroblast growth factors, 10–11, 14, 97t
Fibrinogen, 257, 354
Fermentable carbohydrates, 213, 220
Fenestrated capillary, 111
Fabry disease, 484t
Extrusive luxation, 386
Extracellular matrix
basement membrane, 73
collagen. See Collagen.
dentin, 9, 440
fibronectin, 73–74
growth factors in, 42
laser capture microdissection of, 9
plaque biofilm formation of, 207
tooth morphogenesis role of, 14–15
Extrusive luxation, 386
F
Fabry disease, 484t
Fenestrated capillary, 111
Fermentable carbohydrates, 213, 220
Fibronectin, 257, 354
Fibroblast(s)
connective tissue remodeling, 79
definition of, 78
functions of, 67
illustration of, 78f
interleukin-1 effects, 264
mitotic activity of, 78
morphology of, 78
substance P effects, 70
Fibroblastic growth factors, 10–11, 14, 97t
Fibroblastin, 39
Fibronectin, 73, 73–74
Fibronectin-binding protein, 333
Fluorescent antibody cell sorting, 96
Fluoride:
caries prevention using, 221–222
dental sensitivity managed using, 189
Foreign bodies, 380, 380f–381f
FBP3+CD25+ cells, 280
Fractures, 385–386
Free radicals, 423–424
Fungi, 231, 376f, 378
Fusobacterium species, 217
G
G proteins, 145
Gap junctions, 76, 136f
Gaucher disease, 482–484, 483f, 483t
Gene regulation, 422
Genetic and developmental disorders
amelogenesis imperfecta, 477
denis in dente, 475f, 475–476
dentinogenesis imperfecta, 16, 17f, 476f, 476–477
Gaucher disease, 482–484, 483f, 483t
hemoglobinopathies, 481–482
hypophosphatemic rickets, 479–481, 481f
sickle cell anemia, 481–482, 482f
tauroidontism, 474, 475f
thalassemia, 481, 482f
German measles, 473–474
glass ionomers
conventional, 337, 337f
description of, 312
resin-modified, 312, 338
Glia, 165
Gli-1
Glia-derived neurotrophic factor, 137
Glossopharyngeal neuralgia, 459–460
Glucocorticoid excess, 485–486
Glucocorticoids, 145
Glycosaminoglycans, 4, 67, 72
Golgi complex, 74–74, 434
G-protein–coupled receptors, 145
Gram-negative bacteria, 227b
Gram-positive bacteria, 227b
Granulocyte colony-stimulating factor, 284
Granulocyte-macrophage colony-stimulating factor, 287
Growth factors
angiogenic, 36
definition of, 10, 77, 97f
dentin matrix, 36
function of, 97f
insulin-like, 36
odontoblast-like cell differentiation induced by, 42
orthodontic therapy effects, 127
regenerative medicine use of, 96–98
types of, 97f
Treatment of, 137
Hageman factor, 488t
Haggard factor, 257
Hartwig’s epithelial root sheath, 397
Hayflick phenomenon, 423
Headache
cluster, 457–458
migraine, 453–457
Healing
bacteria effects on, 302–303
with cementum, 402
ossous replacement for, 402–403, 403f
Heat shock proteins, 335, 432
Hedgehog signaling, 401–402
Heparanase, 380
Hemorrhage control, 305–306
Hemoglobinopathies, 481–482
Helper T cells, 79, 278, 280, 291–292
Hemoglobin, 39
Hemostatic cascade, 255–259
Hemostasis, 256
Hemostatic response, 166–167
Histiocytes
macrophages, 81–82
dendritic cells, 82–84
regulatory mechanisms, 168–169
HMG-CoA reductase, 37
Honey bee venom, 37
Hyperalgesia, 148
Hydroxyapatite crystals
immobilization of, 31
Environmental effects of, 260–262
Hydroxyapatite crystals
hydrothermal treatment of, 32
Hydroxyapatite crystals
induced deposition, 31
Hydroxyapatite crystals
organic components of, 30
Hydroxyapatite crystals
porogen substitution of, 32
Hydroxyapatite crystals
seedling response of, 31
Hydroxyapatite crystals
substitution of, 31
Hydroxyapatite crystals
treatment of, 137
Hyperthyroidism, 479
Hypocalcemia, 479–481
Hypocalcemia, 479–481
Hypersensitivity:
class I, 193–194
innate, 283–285
periapical, 277–282
immune, 277
Immunocompetent cells
inflammatory-induced response, 85–86
cavity preparation and restoration effects, 84–85
dentin cells, 82–84
lymphocytes, 79–81
macrophages, 81–82
Immunodeficiencies
description of, 203
innate responses, 283–285
specific responses, 285–287
Immunoglobulins, 270, 281, 426
Indirect pulp capping, 317–319
Inflammation
in children, 166–167
restorative materials and treatments that cause, 343f
root resorption induced by, 401–402
Inflammatory cyst, 381f
Inflammatory mediators
chemokines, 269
cytokines, 263–264, 266–269
See also Cytokines.
defensins, 270
description of, 127–128, 241
function of, 241
histamine, 123, 242
immunoglobulins, 270
mucleotides, 270
microcirculatory system effects, 127–128
nerve functions affected by, 171–172
neuropeptides, 243–244, 354
nitric oxide, 261, 261–262, 355
nociceptors sensitized by, 160
nucleotide-binding oligomerization domains, 267–268
odontoblast production of, 242
oxytocin–derived free radicals, 262–263
periapical, 287–293
plasma proteases
clotting system, 257–259
complement system, 256–257
fibrolytic systems, 257–259
kinin system, 256
lysozyme enzymes, 260–261
matrix metalloproteinases, 260–261
protease inhibitors, 261
platelet-activating factor, 256
proteins, 255
regulatory mechanisms, 168–169
resolins, 255
root resorption, 399
serotonin, 242–243
Inflammatory pain
characteristics of, 166–177
nonsteroidal anti-inflammatory drugs for, 193–194
innate immunity
innate immunity and, transition between, 329
deficiencies in, 283–285
description of, 277
Irreversible pulpitis, 450–451
Ion channels, 145–147
Intratubular dentin, 49, 440
Intraradicular infections
Intraluminal collagen, 51f
Intertubular dentin, 32, 49, 440
Interstitial space, 114
Interstitial pressure
Root resorption, internal. See Internal root resorption.
Interleukin-11, 288, 399–400
Interleukin-8, 287
Interleukin-6, 268–269, 287–288, 399
Interleukin-2, 268, 287–289
Interleukin-4, 288
Intercellular cell adhesion molecules, 248, 250
Integrins, 77, 250, 397
Intercellular cell adhesion molecules, 248, 250
Interleukin-11, 288, 399–400
Intertubular dentin, 32, 49, 440
Intraluminal collagen, 51f
Intraradicular infections
persistent, 225b, 232–234
primary characteristics of, 225b, 226
description of, 225–226
geographic influences, 228–229
microbiota associated with, 226–228, 227b, 228, 230
secondary, 225b, 232–234
Intertubular dentin, 49, 440
Ion channels, 145–147
Intracanal irrigants, 100, 235
Intraoral bleaching, 410
Intraluminal injection, 212
of, local anesthetics, 198
Intraluminal collagen, 51f
Intraradicular infections
continuous, 460–462
definition of, 458
description of, 174–175, 175f
episodic, 458
Neuropeptide Y, 119, 120f, 143, 243, 245–246, 354
Neuropeptides, 122f, 143, 243–247, 354, 434
Neuropil interactions
agents involved in, 138b
schematic diagram of, 134f
Neurophils, 262, 283b
Niches, 93
Nitrin oxide, 261f, 261–262, 355
Nociceptors
central sensitization activated by, 172
drugs that block release or actions of inflammatory mediators, 192–195
interneurons effect, 163, 163f
neurophysiology of, 147–153
sensitization of, 170
signal transmission pathways, 160–166
Nodes of Ranvier, 146
Noncollagenous proteins, 18, 18t
Nonodontogenic pain
atypical odontalgia, 461–462
cardiac origin of, 462–463
causes of, 451–453
clinical features of, 452b
cluster headache, 457–458
Pulp 
Proteoglycans
Protein kinases, 164
Prosthetic procedures, 125–126

Pulp capping
Projection neurons, 163–164

See cellular arrangement of, 68f, 68–69
caries-induced exposure of, 224, 224f
biology of, 21–22
adhesion molecules in, 247–248, 250
structure of, 72
hydrophilicity of, 72
definition of, 67
bacterial penetration prevented by, 73

materials for
indirect, 317–319
exposure duration effects on, 303

dentin bridge effects on, 306–307
dentin bridge formation as indication of, 43
adhesive systems for, 312–313

Vital pulp.
See Microcirculatory system.
See vascular responses of, 242
tissue engineering of, 103
size reductions in, 438
sensory innervation of, 70
revascularization of, 407
responses of, 277–278

dentin; Pulp.

See also
Pulpitis
Pulpal nerves
Pulpal interstitial pressure, 115–116

Tooth injury.
See also
Endodontic infections.

Caries.

stimulation of, 61
sensory nerve denervation effects on, 121f
parasympathetic nerves, 120–121
paracrine factors, 123
neurotransmitters, 122
peptidergic afferent fibers, 121–123

schematic diagram of, 115f, 117f
sympathetic nerves, 118–120
trigeminal sensory nerves, 126
restorative procedures in effect on, 125–126
sensory nerve denervation effects on, 121f
stimulation of, 61

Pulp infection. See also Endodontic infections.
caries. See also Tooth injury.
cavity preparation as cause of, 334–335
definition of, 77–78
healing after, 302–303
microleakage, 343
pulp capping for. See Pulp capping.
reasons for, 301
root resorption caused by, 402–403
signaling molecules contributing to, 43f
Pulpal nerves
degeneration of, 147
sensory functions of, 148–150, 152–153

Pulpitis
immune cells in, 277–278
management of, 190–199

opioids for, 198
pain caused by, 147, 190–199
silent, 147

Pulpodontal complex. See also Dentin; Pulp.

age-related changes in, 427, 440–442
caries
defense responses to, 329–331, 330f–331f
description of, 325
injury responses to, 328–329
responses to, 328–333
characteristics of, 69–70, 223
defense responses by, 329–331, 330f–331f
definition of, 1
functions of, 91
injury response to caries, 328–329
cavity preparation, 334
description of, 77–78
neuroanatomical responses, 141
signaling molecules contributing to, 43f
stimuli that cause, 139
summary of, 344–345
permeability of, 324–325

repair capacity of, 334
structure of, 47–48, 48f, 324–325

Pulse oximetry, 128

Quorum sensing, 208–209

Radiographs
aging, 441
apical periodontitis, 206f
caries, 218, 218f
external root resorption, 413, 414f, 415
internal root resorption, 412–413, 412f, 415
Raman spectroscopy, 431
RANKL, 282, 399, 401, 477–478

Reactivey dentin
cavity etching stimulation of, 38
cellular signaling of, 38
definition of, 34, 78
deposition areas for, 334
ethylene diaminetetraacetic acid effects, 38
production of, 333
remaining dental thickness effects, 37–38
restorative materials’ effect on formation of, 342–343

Reactivey dentinogenesis
biochemical processes, 35f–36f, 35–37
definition of, 35, 331, 333
factors that affect, 37–38
histomorphometric findings, 37–38
odontoblast upregulation during, 35–37
restorative materials that cause, 35–36

Reactive oxygen species, 423
Receptor activator of nuclear factor κB ligand. See RANKL.
Recombinant human bone morphogenetic proteins, 91, 310
Recombinant human insulin-like growth factor 1, 97–98
Recurrent caries, 211–212, 218–219
Referred pain, 176–177, 447–448, 448f–449f
Regeneration
definition of, 92
history of, 91
homeostatic, 91
injury-induced, 91

Regenerative endodontology
challenges associated with, 104
delivery improvements for, 103–104
dental pulp constructs for, 98–100, 99, 102
objectives of, 92
outcome measurements, 104
postnatal stem cells for, 98–99, 99, 102
research priorities for, 102–104
root canal revascularization using blood clotting, 100–101, 102

Regenerative medicine
foundations of, 92–98
growth factors, 96–98
history of, 91
progenitor cells, 92–95
stem cells. See Stem cells.
Regulatory T cells, 278, 280, 291
Remaining caries, 212
Remaining dentinal thickness, 37–38, 325, 334–335, 355
Remineralization
description of, 212
fluoride effects on, 222
Renal dystrophy, 415
Reparative dentin, 34, 78, 308
Reparative dentinogenesis
biochemical processes during, 35f
collagen fibrils in, 72
definition of, 333
dentin bridge formation vs, 43
description of, 38
fibrodentin matrix secreted before, 39
histologic findings, 39f
matrices secreted during, 38, 39f–40ff
odontoblast-like cell differentiation, 41–43
progenitor cell recruitment in, 40–41
tertiary dentinogenesis and, 39
Reparative tertiary dentinogenesis, 316
Replicative senescence, 423
Resident cells, 282
Resin-based materials, 335–337, 336f–337f
Resin-modified glass ionomers, 312, 338
Resolsina, 235
Restorative dentistry, 323
Restorative materials and procedures
bacterial microleakage, 303, 343
calcium hydroxide. See Calcium hydroxide.
dentin permeability effects, 61–62
inflammation caused by, 343f
microcirculatory effect, 125–126
mineral trioxide aggregate, 313–315, 315f
odontoblast survival affected by, 341–342
physical properties of, 349–351
reactive dentin formation affected by, 342–343
specific heat of, 349–350
tertiary dentinogenesis effects, 39
reactionary dentin formation affected by, 342–343
physical properties of, 349–351
reactive dentin formation affected by, 342–343
specific heat of, 349–350
tertiary dentinogenesis effects, 35–36
thermal conductivity of, 349
thermal diffusivity of, 350
tooth-colored, 344
thermal diffusivity of, 350
thermal conductivity of, 349
tertiary dentinogenesis effects, 35–36
reactionary dentin formation affected by, 342–343
physical properties of, 349–351
reactive dentin formation affected by, 342–343
specific heat of, 349–350
tertiary dentinogenesis effects, 35–36
thermal conductivity of, 349
thermal diffusivity of, 350

tag tooth, 412, 415
radiographic findings, 412–413, 412f, 415
treatment of, 412–413
vitality testing, 415
mechanisms of, 397–401
misdiagnoses, 415
Paget disease of bone and, 415. See also Pulp. Paget disease of bone.
pulpal role in, 401–402
renal dystrophy and, 415
requirements for, 401
resistance to, 397–398
subepithelial inflammatory, 408–410, 415
systemic causes of, 415–416
Rubella, 473–474, 474f
Ruby lasers, 361
Ruffini mechanoreceptors, 135
Russel hyaline bodies, 383, 383f
Russell bodies, 382f, 382–383
S
Saliva, 218, 220, 222
Scaffolds, 99–100, 102
Sclerotic dentin
description of, 327
illustration of, 328
permeability of, 56
Secondary caries, 211
Secondary dentin, 27, 33–34, 48–49, 78, 430, 433, 439, 440
Selectins, 248
Self-etching adhesives, 336
Senescence, 421–423
Sensory fibers
See Dentinal sensitivity.
Sensory fibers
injury responses of, 139
odontoblast and, interactions between, 138
Sensory neurons, 134f, 134–135, 434
Serotonin, 242–243
Severe combined immunodeficiency, 285–286
Shingles, 473
Sickle cell anemia, 464, 481–482, 482f
Silent pulpitis, 147
Single-bottle adhesive systems, 336
Sinus headache, 454
Sinusitis, 455, 460
Small integrin-binding ligand, N-linked glyco-
protein family, 18
Smear layers
creation of, 57, 335
description of, 57
illustration of, 58f
permeability effects, 58
pulp stem cell attachment to, 102, 103f
removal of, 103, 341
treatment of, 58
Smear plugs, 57
Smooth surface caries, 216f
Sodium channels, 146
Sodium hydroxide, 235
Somatoform pain disorder, 464
Specific plaque hypothesis, 212
Spiriches, 378
Starling forces, 114–115, 116
Stellate reticulum, 4
Stem cells, 41
advantages of, 94–95
allogeneic, 95
from apical papilla, 95
autologous, 94–95, 104
definition of, 92
developmental stages of, 94f
differentiation of, 7
embryonic, 93–94
from human exfoliated deciduous teeth, 7, 7f
isolation and identification of, 96
niches of, 93
osteogenic induction of, 7f
overview of, 91–92
periodontal ligament–derived, 7, 7f
postnatal, 93–94, 98
protein expression by, 96
pulp. See Pulp stem cells.
source-based classification of, 94
tooth-derived, 6–7, 7f
umbilical cord, 94
xenogeneic, 95
Stemcellidomatoid muscle, 454f
Stratum intermedium, 4
Streptococcus mutans, 214
Subepithelial inflammatory root resorption,
408–410, 415
Subluxation, 386
Substance P, 70, 121–123, 243–247, 334
Sulcular infection, 408–410
Suppressor T cells, 291
Sym pathetic nerves
pulpal blood flow regulated by, 118–120
tooth innervation by, 119f, 138
Systemic disorders
herpesvirus infections, 472–473, 473f
human immunodeficiency virus, 471–472
nonodontogenic pain caused by, 464–465
Paget disease, 478–479, 479f
rubella, 473–474, 474f
T
T cells, 283b
caries-induced response, 85–86
CD4+, 279
CD8+, 279
cytotoxic, 278
description of, 79–80
helper, 278, 280, 291
illustration of, 80f
mechanism of activation, 80
natural killer, 280
regulatory, 278, 280, 291
suppressor, 291
Taurodontism, 474, 475b, 475f
Telomeres, 428–429, 431
Temporalis muscle, 454f
Teratoma, 283f
Terminal capillary network, 68
Tertiary dentinogenesis
cavity preparation materials that affect,
35–36
description of, 34–35
repairative, 316
transforming growth factor-β1’s role in, 36
Thalassemia, 481, 482f
Thermal allodynia, 449
Thermal stimuli
cavity preparation, 395–393
laser treatment, 358–366
Thromboxanes, 251–252
Tight-junction capillary, 111
Tissue development stages, 94f
Tissue engineering
definition of, 92
pulp, 103
scaffolds for, 99–100
Toll-like receptors, 77, 102, 266f–267f, 266–267,
282, 287–288, 329
tooth bleaching, 367
Tooth development
description of, 1–2
enamel knots, 14
epithelial-mesenchymal signaling interactions
during, 10f
experimental systems for
description of, 4
knockout mice, 7–8
laser capture microdissection, 9
tooth organ culture systems, 4–6, 5f
transgenic mice, 7–8
Transgenic mice studies of, 8
Transgenic mice development of, 7–8
Tooth development studies using, 7f, 7–8
Tooth injury. See also Pulpal injury
axonal degeneration secondary to, 147
cytochemical responses to, 139–145
delayed neural reactions to, 141
human teeth studies of, 141–142
ion channels, 145–147
membrane receptors, 145–147
stimuli that cause, 139
structural responses to, 139–145
trigeminal nerve and ganglion plasticity, 140–141
Tooth injury and pain, 4
Tooth organ culture systems, 4–6, 5f
Toothache, odontogenic, 449b, 450f, 451
Tooth-colored restorative materials, 344
Tooth-derived stem cell lines, 6–7, 7f
Tooth-signaling molecules, 1
Transcapillary exchange, 114–115
Transcription factors
  core-binding factor a1, 12, 13f
definition of, 10
function of, 10
Transdental permeability, 55f
Transforming growth factor-a, 97t
Transforming growth factor-β, 97t
Transforming growth factor-β1, 430
chemotactic role of, 41
etchants that solubilize, 36
inflammatory role of, 269
odontoblast secretion, 33
odontoblast-like cell differentiation induced by, 41–42, 42f
production of, 293
reactionary dentinogenesis role of, 36
receptors, 38
Vascular cell adhesion molecule, 248
Vascular endothelial growth factor, 329
Vasoactive intestinal peptide, 120–121, 143, 243
Vasoactive neuropeptides, 329
Vasoconstrictors, 124
Veillonella species, 214
Venules, 111
Viruses, 231–232, 379
Vital pulp
  external root resorption prevented by maintenance of, 407
testing of
description of, 178–180
root resorption diagnosis, 415
Vital pulp therapy. See also Pulp capping
dentin adhesives for, 312–313
dentin bridge effects, 306–307
description of, 301
mineral trioxide aggregate for, 313–315, 315f
resin-modified glass ionomers for, 312
Vitamin D metabolism disorders, 479–481
Vitamin D-dependent rickets, 479–480
Voltage-gated ion channels, 145
W
Wide dynamic range projection neurons, 164
X
Xenogeneic stem cells, 95
X-linked hypophosphatemic rickets, 479–481, 481f
Z
Zinc oxide-eugenol, 318
Zone of destruction, 216, 217f
Zone of Höhl, 96
Zone of Weil, 68, 113
Zoster, 473, 473f