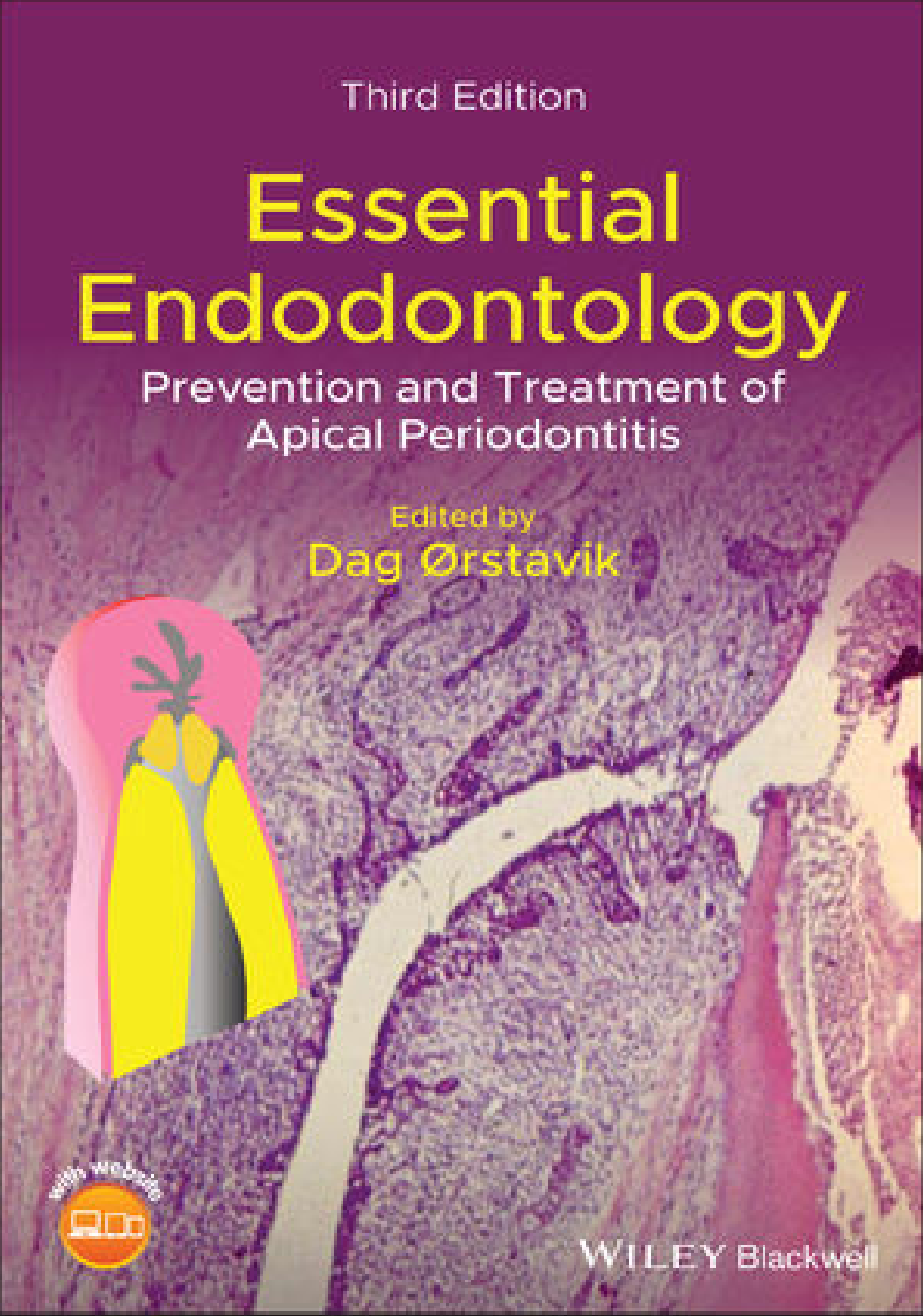
Third Edition

Essential Endodontology

Prevention and Treatment of Apical Periodontitis

Edited by

Dag Ørstavik



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Foreword

Two infections affect the survival of teeth: those of the gingival/periodontal and pulpal/apical periodontal tissues. The pain and loss of function that come with severe forms of either disease may also severely impair the quality of life in affected individuals. Infections of the pulp and periapical tissues belong to the domain of endodontology. While other conditions and diseases form important part of the discipline, treatment of teeth with pulpitis or apical periodontitis by root fillings or apical surgery constitute by far the most important part.

Essential Endodontology seeks to integrate basic, biological, and microbiological knowledge of apical periodontitis with diagnostic and treatment practices. The emphasis of the book remains the same as before. It focuses on the biology and clinical features of endodontology's most important disease in order to promote ever better approaches to its diagnosis, prevention, and therapy.

One might ask if there is still a need for textbooks of this kind. Any student or practitioner can access the most advanced, novel techniques and methods, as well as scientific publications, directly on social media or from public databases. However, one may argue that there is an even greater need for the more advanced, basic text today than before. The figure illustrates the explosion in the number of publications related to endodontics in recent years. In the decade leading up to the second edition in 2008, the number of new endodontic publications was up by 38 per cent from the decade before. In the next 10 years, the increase was 125 per cent, totaling 14,685 publications.

It is clear that the total scientific contributions to the discipline now far outnumbers

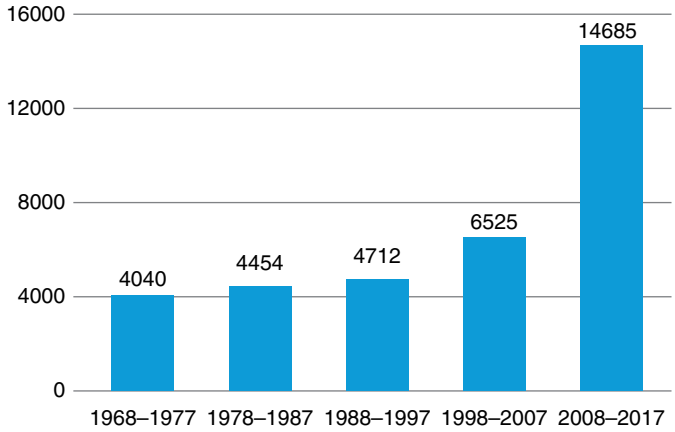

Figure: The number of publications listed in PubMed (US National Library of Medicine, National Institutes of Health) with the search term "endodontics" during the past five decades.

what any researcher, scientist, or clinician can possibly read or absorb. It is also impossible for a novice in the field to navigate in an area where the quality of available information will be highly variable. Thus, a compressed basis of knowledge provided by experts in their fields is essential as a starting point for further studies, and provides a backbone of knowledge and insights. The target audience for the book remains postgraduate students, teachers, and researchers focusing on endodontology. *Essential Endodontology* will also serve as a supplement for undergraduate students of endodontics.

The 2008 edition was hardly a year out in print before the co-editor of both previous editions, Thomas R. Pitt Ford, passed away. His contributions to the previous two editions were a *sine qua non* for their completion, and his professional and personal qualities were sorely missed in the preparation of this third edition. I hope that the reader will find the spirit from the previous editions prevailing in the present, and recognize the focus on quality and depth that was Tom Pitt Ford's hallmark.

Dag Ørstavik

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The website contains downloadable figures from the book.

1

Apical Periodontitis

Microbial Infection and Host Responses

Dag Ørstavik

1.1 Introduction

Endodontology includes pulp and periapical biology and pathology. As a clinical discipline, however, endodontics mainly deals with treatment of the root canal and the placement of a root filling, or treatment by surgical endodontics. The technical procedures associated with treatment focus on the particular problems of asepsis and disinfection of the pulp canal system. Treatment measures to preserve pulp vitality are a shared responsibility with conservative dentistry, and include specific techniques in dental traumatology. Recent research has shown the importance of asepsis and disinfection procedures also for treatment of pulps exposed by caries or trauma, extending classical endodontic treatment principles to the management of deep caries (see Chapter 9).

For vital teeth requiring partial or full pulp removal, the initial diagnoses and the difficulties associated with treatment may be related to the state of the pulp, but the purpose of treatment is no longer the preservation of the pulp but the prevention and/or elimination of infection in the root canal system. The ultimate biological aim of this treatment is to *prevent apical periodontitis*. For teeth with infected/necrotic pulpal with an established apical disease process, the biological aim is to *cure apical periodontitis*. Of the endodontic diseases, apical periodontitis is therefore prominent as it is a primary indication for root canal treatment and because it is by far the most common sequel when treatment is inadequate or fails (Figure 1.1). Even the measures taken to preserve pulp vitality may be viewed as ultimately preventing root canal infection and the development of apical periodontitis.

The importance of microbes in the initiation, development and persistence of apical periodontitis has been thoroughly documented (see Chapter 4). The emphasis in this book is on the infectious etiology of apical periodontitis and on the aseptic and antiseptic principles applied during treatment. Furthermore, new research findings have impact on aspects of diagnosis, treatment, prognosis and evaluation of outcome in endodontics. It is therefore important to use the acquired knowledge to build treatment principles logically, and to show how all these fundamental aspects can be applied in clinical practice.

1.2 Terminology

Both pulp and pulp-periodontal diseases have been subject to many classification systems with variable terminology. Periodontitis caused by infection of the pulp canal system has been termed apical periodontitis, apical granuloma/cyst, periapical osteitis and

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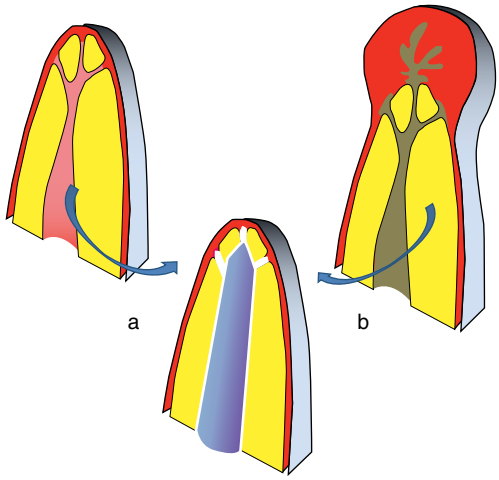

Figure 1.1 Pulp extirpation (a) prevents and root canal disinfection (b) cures apical periodontitis. Both need a root filling of the entire pulpal space.

Table 1.1 Classification of apical periodontitis [18].

AAE	ICD-10
Symptomatic apical periodontitis SAP[1]	K04.4 Acute apical periodontitis of pulpal origin[2]
Asymptomatic apical periodontitis AAP	K04.5 Chronic apical periodontitis
Chronic apical abscess	K04.6 Periapical abscess with sinus[3]
Acute apical abscess	K04.7 Periapical abscess without sinus
Condensing osteitis[4]	
Radicular cyst	K04.8 Radicular cyst

[1] presents with a broad range of symptoms
[2] presents with strong pain
[3] further subdivided in relation to sinus tract location on surfaces
[4] may be seen as a variant of AAP or Chronic apical periodontitis

periradicular periodontitis, among other terms. Sub-classifications have been acute/chronic, exacerbating/Phoenix abscess and symptomatic/asymptomatic, among others [18]. The two most accepted classification schemes are presented in Table 1.1. These are quite similar, but symptomatic teeth according to the AAE classification may include more cases than teeth with acute apical periodontitis according to the ICD. The latter term is for cases presenting with subjective needs for immediate treatment, while symptomatic teeth may include teeth that only slightly affect the patients and that are diagnosed by chairside testing (see Chapter 7). The term "chronic" is useful for prognostication and follow-up studies: symptomatic or not, it implies the presence of a radiolucent lesion, which is a major predictor for treatment success [24]. The term "symptomatic" confirms that there are objective signs verifying the diagnosis.

Apical periodontitis includes dental abscess, granuloma and radicular cyst as manifestations of the same basic disease. The balance between the virulence and extent of infection on the one hand and the body's response on the other, determines whether the condition is symptomatic/acute versus asymptomatic/chronic. The historical emphasis on the differential diagnosis of a cyst versus a granuloma has been abandoned. This is due to the fact that radiographs, even from CBCT, are not very sensitive in discriminating between cysts and granulomas [6]; they share the same etiology and basic disease processes (Chapters 3 and 4); and their treatment and prognosis are also similar (Chapters 11 and 12). However, so-called true cysts separated from the root canal infection that initiated them may show impaired healing [27] and require surgical removal, but there are no means for diagnosing such cases without scrupulous histological investigation of surgical biopsies [32].

Terminology should not be considered a straitjacket for authors or clinicians. Therefore, variants of the terms and references to other diagnostic schemes, in this book and other texts, are inevitable, and can even be desirable. However, given that insurance companies and other third parties require codes or terms for reimbursements, and legal issues dictate clear basic diagnoses as basis for treatment, selection and proper usage of a recognized classification scheme is mandatory.

1.3 Pulp Infection and Periapical Inflammation

The oral cavity is an extension of the skin/mucosal barrier to the external environment. In the digestive tract, it may be viewed as the first battleground for the body's efforts to maintain homeostasis and keep infection away from the vulnerable interior parts of the body. Infection occurs when pathogenic or opportunistic microorganisms infiltrate or penetrate the body surface. In the oral/dental sphere, the body surface is either the mucosa or the enamel/dentine coverage of underlying soft tissue. Endodontic treatment aims to re-establish the muco-cutaneo-odonto-barrier with a complete seal from the coronal to the apical end of the treated root, whereas voids or leaks in the restoration may present an opportunity for bacteria to establish themselves close and eventually ingress into the body's interior. The emphasis on coronal as much as apical leakage of bacteria and bacterial products reflects this line of reasoning.

The evolution of permanent teeth in a dentition with multiple functions is integral to the evolution of animals [40], not least primates and man. However, the structure of these teeth is such that if fracture occurs, microorganisms may enter the body and establish a foothold in the exposed dentinal and pulpal tissues. Unless protective mechanisms were developed, such infections would be life-threatening and presented a strong survival disadvantage in the young [40]. Employing and modifying general mechanisms of inflammation, apical periodontitis evolved to combat and contain the infections in the compromised dental pulp spreading through its ramifications and the tubules of dentin (Figure 1.2). While defining the disease, apical periodontitis works therefore to our advantage; it is the underlying infection that is the cause for concern.

The protection by tissue responses comes at a cost, however. Clinical symptoms that accompany the inflammation may be distressing to the patient, and the granuloma or cyst are not always effective in containing the invading microbes. The pain sometimes following the inflammation of the pulp and periapical tissues can be excruciating and is a testimony to the potential danger of the infection. This pain is also the starting point for human attempts to combat dental disease. Thus, acute pulpal and periapical inflammation were the among the first targets of the dental profession.

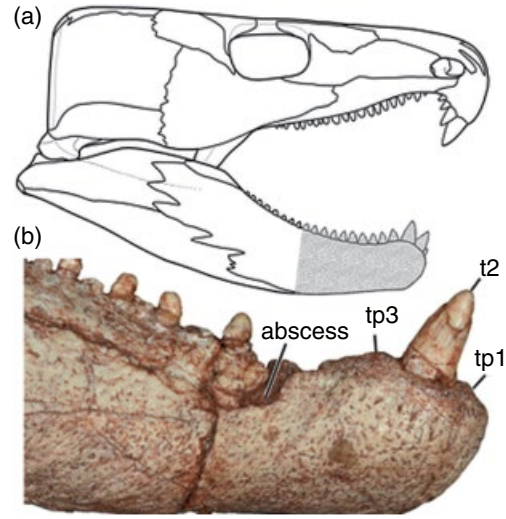

Figure 1.2 Evidence of dental and mandibular pathology in Labidosaurus hamatus, a basal reptile from the Lower Permian of Oklahoma. (a) Skull reconstruction in right lateral view. (b) right hemi-mandible in lateral view. Reproduced with permission from [40].

Teeth, cheek cells, tongue crypts, tonsillar irregularities, gingival sulci and other anatomical structures are safe havens for microbial populations of the mouth. From these areas, microbes of varying virulence may emigrate and cause infections such as tonsillitis, gingivitis, pericoronitis, marginal periodontitis, dental caries, pulpitis and apical periodontitis. Whereas physiological and mechanical cleansing activities tend to reduce the level of microorganisms in the mouth, environmental factors sometimes favor infection rather than its prevention. Current research on oral microbial communities emphasizes the

concept of biofilm formation and development, with particular physiological, genetic and pathogenic properties of the organisms expressed as consequences of the conditions within the biofilm (see Chapter 4).

Caries has been the dominant dental infection for decades, and infection and inflammation of the pulp and periapical tissues are often an extension of the dental caries process. Researchers studied the occurrence and epidemiology of apical periodontitis as part of caries investigations. The infectious nature and the possibilities for spreading and complications of apical periodontitis should form the basis for independent surveys of public health consequences of endodontic diseases.

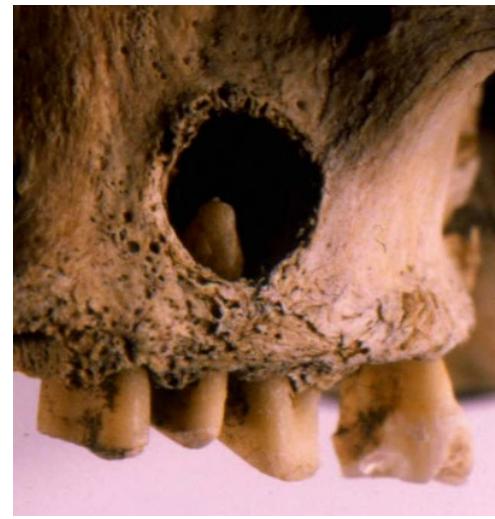

Figure 1.3 Apical periodontitis in an upper premolar of a woman's skull found in Iceland and dating to the 12th century. Trauma or wear caused exposure of the pulp with infection and lesion development.

1.4 Biological and Clinical Significance of Apical Periodontitis

1.4.1 Apical Periodontitis as an Infection

Root canal infections and apical periodontitis is common today and is a frequent finding in skulls from archaeological investigations (Figure 1.3). In the pre-antibiotic era, infections of the pulp and periapical tissues were potentially serious and needed close monitoring. In the early days of antibiotics, it was found that most of these infections were readily susceptible to penicillin, and therefore the spread of infection to regional spaces was often controllable by antibiotics. Today, it is recognized that pulp infection may be caused by organisms of different virulence (see Chapter 4), and that control of the infection is not always easily accomplished.

The flora of the mouth fortunately has relatively few pathogenic organisms, which usually have low virulence. Most are opportunistic, causing disease only in mixed infections or in hosts compromised by other diseases. However, organisms that are not normally pathogenic in the oral cavity may exhibit features of virulence if allowed access to the pulp or periapical tissues. Studies of the infected pulp have shown the presence of oral bacteria that normally inhabit the mouth, which do not normally cause disease. The apical periodontitis response to pulp infection may be viewed as a way of taming and coping with expressions of virulence by the infecting organisms. Thus, the pain frequently encountered in the early stages of disease development usually subsides in response to the tissue reactions. Furthermore, the initial expansion of the lesion of apical periodontitis is soon followed by periods of quiescence, possibly even regression or at least consolidation of the lesion. This dynamic process is accompanied in time by changes in the composition of the flora recoverable from the root canal.

Some forms of apical periodontitis have been associated with particular species dominating in the pulp canal flora. However, evidence from molecular analysis implies that endodontic infections may be more opportunistic than specific, and include many more species than previously thought (Chapter 4). Research into microbiological causes and interactions in apical periodontitis are imperative for improvements in diagnosis

and treatment. Particularly, this would apply to the so-called "therapy-resistant" cases of apical periodontitis, in which infection persists despite apparently adequate root canal treatment, and to retreatment cases. Modern microbiological techniques have demonstrated an almost endless complexity and variability of the endodontic infections [19, 53], opening new avenues for research and expanding our understanding of the disease.

1.4.2 Infection Control

The outcome of endodontic treatment is dependent on use of an aseptic technique and antiseptic measures to prevent and/or eliminate infection. However, the critical role of infection control may not always be given the prominence it deserves. The transmission of hepatitis viruses has been an issue for a long time, and there is concern about prion transmission via contaminated instruments. The sterilization procedures for contaminated endodontic instruments have limitations, so there is a strong tendency towards applying single-use instruments. Most contemporary, machine-operated instruments are designed for single use, a practice that benefits the local treatment and prevents cross-infections.

1.4.3 Microbial Specificity and Host Defense

The host responses to root canal infection have been the subject of much research. There is great similarity between the pathogenic processes in marginal and apical periodontitis, many of the findings in periodontal research have direct relevance to apical periodontitis. Our understanding of the immunological processes involved in the development of apical periodontitis is expanding (Chapter 3). Microbiological variability and virulence factors in infected root canals have been demonstrated, and the bacterial flora may vary with the clinical condition of the tooth involved (persistent infection, therapy-resistant infection) (Chapters 4 and 11). Thus, different strategies of antimicrobial measures may be possible and even desirable depending on the microbiological diagnosis in a given case.

Reports of apical periodontitis with particularly aggressive microbes are fortunately very rare. Root canal infections with bacteria causing necrotizing fasciitis have been reported with very serious, even life-threatening consequences [48], and bacteria with resistance to common antibiotics may pose a problem, particularly in patients with impaired immune system [5]. However, it is important to remember that incomplete and inadequate root canal treatment can lead to infections requiring hospitalization and extensive medical treatment [17].

1.4.4 Endodontic Infection and General Health

The focal infection theory has been a source of both frustration and inspiration in dental practice and research. Both irrelevant and sometimes incorrect arguments and concepts were used to dictate an unnecessary wave of tooth extractions in healthy individuals for decades. Unsubstantiated opinions on the subject restricted clinical developments in the field of endodontics for a very long time. The controversy, however, has also sparked important new discoveries, and it is, even today, an important part of the frame of reference in studies of endodontic microbiology and host defense mechanisms.

1.4.4.1 Influence of General Health on Apical Periodontitis

Apical periodontitis and other disease processes may mutually affect each other. The root canal infection meets a response that is defined by the host's condition and dependent on genetic and constitutional factors, including systemic diseases. This variable tissue response may limit or allow expansion of the apical lesion, and it may promote or impair healing responses during and after treatment of the infection.

Diabetes is the classical example: it causes a general, reduced defense against infections and diabetic patients may have more and larger lesions [41, 45].

Smoking has a general, adverse effect on infection defenses and affects marginal periodontitis and wound healing negatively; it may also affect the incidence and healing rate of apical periodontitis [25, 36], but the effect may be weak or questionable [42], and confounding factors (age, marginal periodontitis) make conclusions about its effect difficult [25].

There is speculation that infection by the *varicella zoster* virus may be causally associated with root resorption and development of apical periodontitis [35, 47], but the evidence is very limited and inconclusive [22]. Similarly, other viral infections have been implicated in the pathogenesis of otherwise bacterially initiated apical periodontitis [20, 21, 26, 29]

Sickle cell anemia may cause pulp necrosis, preferentially in the mandible, apparently in the absence of microbial infection [12]. Subsequent infection causes classic apical periodontitis. The mechanisms for this increased susceptibility are poorly understood, but patients express high levels of genes for inflammatory cytokines [13]

Systemic medicaments influencing the immune and host response status in patients will influence the biological processes associated with apical periodontitis as well [9]. Moreover, as study designs and research methodologies become more sophisticated, dental diseases are found to be linked with diseases in other locations. Patients with inflammatory bowel disease have a higher prevalence of apical periodontitis and their lesions are larger [37], as they are in diabetic patients with poor glycemic control. Immunosuppressive medicaments generally, or the diseases for which they are used, may not influence healing after endodontic treatment significantly [2, 33]. Other medicaments may favor healing; one study found that statin intake improved the incidence of healing after endodontic therapy [1].

There is a well-establish relationship of marginal periodontitis and preeclampsia and preterm births [34], which is traditionally linked with a raised level of inflammatory blood markers [10, 50]. Similarly, preeclampsia occurs more frequently in the presence of apical periodontitis [23].

Antimicrobial and pain-relieving medicaments have their place in treatment of apical periodontitis. However, when applied for other indications, they may mask symptoms [38], possibly impair body defenses [52] and the microbial population may develop resistance to the antibiotics.

Patients treated with immunosuppressants or who otherwise have compromised immune systems need special consideration. A number of the blood dyscrasias, notably leukemias, are associated with potentially serious sequels to apical periodontitis: infection spreads easily and may require extensive antimicrobial therapy. *The irradiated patient* is a special case: the incidence of osteoradionecrosis [8] after oral surgical procedures places high demands on effective, conservative treatment of endodontic conditions. Similarly, patients on bisphosphonate therapy by intravenous injections may be at risk for tissue necrosis after surgical endodontics [31]. Case reports of complications from endodontic therapy in patients with reduced resistance [5, 46] point to the importance of meticulous and complete endodontic treatment in such patients.

1.4.4.2 Apical Periodontitis Affecting Other Tissues and Organs

Distant and systemic consequences of apical periodontitis is the other side of the coin.

Sinusitis may be induced by root canal infections of maxillary molars or, in very few instances, second premolars [49]. In the lower jaw, inflammation may cause paresthesia of the mandibular or mental nerve. These complications normally subside after successful treatment of the affected tooth [51].

Generally, any disease for which bacteremia poses an additional hazard is of concern in endodontics. Particularly, a history of infective endocarditis, congenital heart disease, rheumatic heart fever or the presence of an artificial heart valve or other susceptible vascular implants may necessitate the

implementation of an antibiotic regimen in conjunction with the endodontic procedures. The magnitude of risk for cardiovascular complications due to bacteremia of dental origin is low and the need to controlling minor and chronic oral infections, including apical periodontitis [39], may be questioned [11]. The formalization of guidelines for antibiotic prophylactic needs by physicians and dentists to ensure safety for patients at risk has made decision making easier [28].

Atherosclerosis is central to the development of cardiovascular disease (CVD) [14]. The arterial plaques may be sites of colonization by microbes circulating during transient bacteremia, and oral infections may thus be a risk factor for CVD [44]. Specifically, apical periodontitis has been associated with an increased incidence of cardiovascular disease events [3, 4, 15, 16, 43]. Research into this association is complicated by a lack of strict criteria for assessing the nature of the periapical infection; radiographic observations give only the status at the time it is taken and cannot discriminate between ongoing infection and a healing lesion. Root-filled teeth, with or without a lesion, may represent a history of pulpitis or apical periodontitis. Pooling all root filled teeth with untreated teeth with apical periodontitis in an individual has been used as a measure of an "endodontic burden"; this is independently associated with CVD [16]. However, viewed isolated from other factors, root-filled teeth are associated with reduced incidence of cardiovascular disease [30]. The chain of events that may give apical periodontitis a role in CVD development is purely conjectural at this stage. However, the blood levels of several cytokines and other compounds associated with CVD are elevated in patients with apical periodontitis [3].

1.4.5 Tooth Loss and Replacement

Untreated apical periodontitis represents a chronic infection of the oral tissues at locations close to many important tissues. While these infections may remain quiescent for decades, they may also develop and spread with serious consequences for the individual. In the face of the risks of such chronic infection from involved teeth, their extraction and replacement by implants has been put forward and discussed as a viable alternative to endodontic treatment. The variable success rates (by strict criteria) of treatment procedures for the cure of apical periodontitis (Chapter 5) are sometimes used as an argument in favor of implants. However, what little evidence is available does not indicate a lower survival rate of endodontically treated teeth [7], and the superiority of tooth preservation compared to its replacement should be stated as a biological principle of preference. The challenge from other treatment options to endodontics as a discipline should act as a driving force to produce more scientifically solid evidence for the modalities of cure and prevention applied to our disease of interest, namely apical periodontitis.

1.5 Concluding Remarks

Pulp and periapical inflammation, the associated pain and the consequences of root canal infection remain significant aspects of dentistry today. New knowledge and insights provide better treatment opportunities and stimulate further research activities. The prevention and control of apical periodontitis has a solid scientific base, but the many variations in the clinical manifestations of the disease still leave technical and biological problems that need to be solved. Technological advances in treatment have made possible effective treatment of teeth that were previously considered untreatable, and further developments in microbiology, host biology and image technology are certain to improve the scientific foundation of endodontology in the near future.

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2

Dentin-Pulp and Periodontal Anatomy and Physiology

Leo Tjäderhane and Susanna Paju

2.1 Introduction

Although dentin and pulp are fundamentally different in that dentin is a mineralized tissue and the pulp is a soft tissue, they are developmentally interdependent and remain anatomically and functionally closely integrated throughout the life of the tooth. Thus, the two tissues are often referred to as the dentin-pulp complex.

Dentin and pulp develop from embryonic connective ectomesenchymal cells from the cranial neural crest during the bell stage of the tooth development (Figure 2.1). The inner dental epithelium of the "bell" encases the condensed mesenchyme. The epithelial-ectomesenchymal interactions initiate the differentiation of the first odontoblasts at the periphery of the dental papilla, and the rest of the mesenchyme will form into future pulp. The differentiating odontoblasts start the secretion of dentin proteins and initiate enamel matrix secretion by ameloblasts [138].

When root formation initiates after crown morphogenesis, Hertwig's epithelial root sheath (HERS) develops from the epithelium at the cuff of the enamel organ. When the HERS grows apically, the adjacent dental papilla cells differentiate into odontoblasts to form root dentin. HERS is critical for root dentin formation: if HERS is disrupted, the dental papilla cells fail to differentiate. On the other hand, cross talk between differentiating odontoblasts and HERS is also necessary for appropriate root formation. The HERS fragmentation allows dental follicle cells to contact the root dentin surface and to differentiate into cementoblasts to form cementum. Also, some of the HERS cells may undergo transition to become cementoblasts. Dental follicle cells secrete collagen fibers that are embedded into the cementum matrix and form the periodontal ligament. Parts of HERS remain in the pulp and in the periodontal connective tissue (Figure 2.2) as epithelial cell rests of Malassez [88, 112, 221]. The formation of lateral root canals and an apical delta of accessory canals rather than a single apical foramen may be a normal variant or it may be due to disturbances of HERS.

The soft tissue of the dental pulp communicates directly with the periodontal ligament (PDL) through the apical foramen or foramina. Sometimes the apical area consists of a delta of accessory canals with several communications between the pulp and the PDL. The rest of the PDL is separated from the pulp-dentin organ by the cementum. Periodontal ligament fibers are embedded in the cementum and alveolar bone as Sharpey's fibers, and attach the teeth to the alveolar bone (Figure 2.3).

2.2 Dentin

Dentin is the largest structural component of human tooth. Dentin provides support to enamel, preventing enamel fractures during

Essential Endodontology: Prevention and Treatment of Apical Periodontitis, Third Edition. Edited by Dag Ørstavik.

Companion website: www.wiley.com/go/orstavik/essentialendodontology

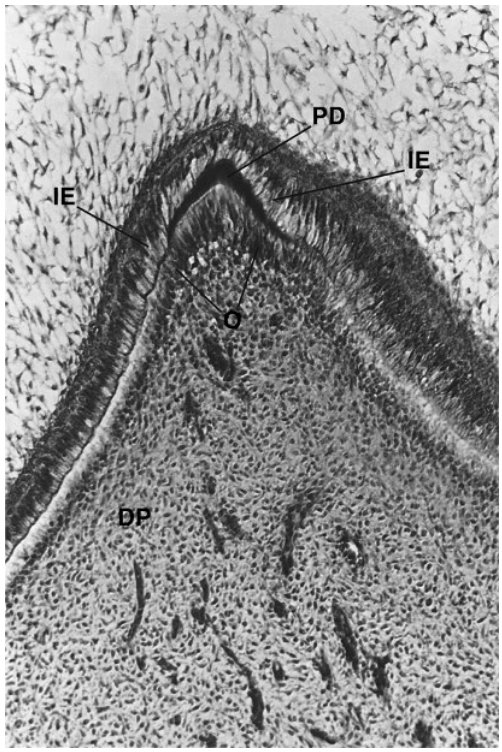


Figure 2.1 Initiation of dentinogenesis at the bell stage of tooth development (DP, dental papilla; O, odontoblasts; PD, predentin; IE, inner dental epithelium).

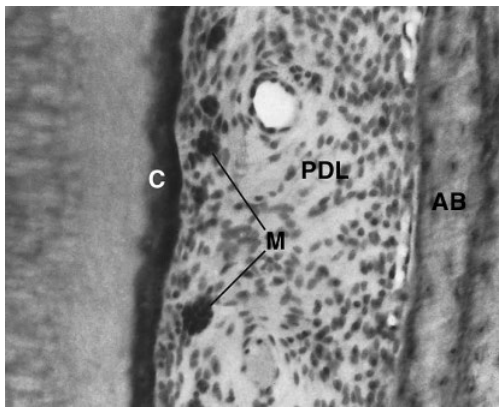


Figure 2.2 Section through the periodontal ligament (PDL) showing Malassez's epithelial rests (M) adjacent to cementum (C) (AB, alveolar bone).

occlusal loading. It also protects the pulp from potentially harmful stimuli and participates in the overall protection of the continuum of the hard and soft tissue often referred as the dentin-pulp complex. Dentin in different locations of a tooth may qualitatively differ from each other, which enables it to meet the requirements in that specific location.

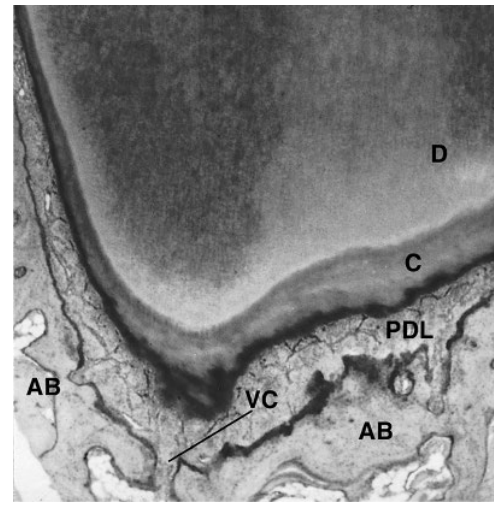


Figure 2.3 The apical portion of a tooth showing alveolar bone (AB), periodontal ligament (PDL), cementum (C), dentin (D), Volkmann's canal (VC).

Dentin is mineralized connective tissue, nanocrystalline-reinforced collagen biocomposite, with unique properties that provide teeth with mechanical strength under heavy occlusal forces. About 70 w-% (55 vol-%) is minerals and 20 w-% (30 vol-%) organic components, the rest being water. However, since the structure of dentin varies within a tooth, these values are only average [208]. About 90% of dentinal organic matrix is highly cross-linked type I collagen, the rest being non-collagenous proteins such as proteoglycans and other proteins, growth factors and enzymes, and small amount of lipids. The mineral is hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), but contains impurities (CO_3, Mg, Na, K, Cl) and fluoride, and should thus be called biological apatite [208].

The major part of dentin is intertubular, formed by the dentin-forming odontoblasts at the dentin-pulp border. Almost the entire dentin organic component is located in intertubular dentin. While forming dentin, odontoblasts leave behind dentinal tubules, in which peritubular dentin is later formed.

Peritubular dentin formation leads to a slow occlusion of tubules. Since peritubular dentin is highly mineralized, the mineral-organic matrix ratio increases from the dentin-pup border towards the dentin-enamel junction, and with age [208, 209].

2.2.1 Dentin Formation

2.2.1.1 Odontoblasts, Predentin and Mineralization Front

Odontoblasts are the outermost cells of the pulp, separated from the rest of the pulp tissue (pulp proper) by a cell-poor layer of Weil. During and immediately after the differentiation the odontoblasts organize into a distinguished odontoblast cell layer, and the mineralization of organic matrix completes the mantle dentin formation [138] (Figure 2.4). In the coronal part of the tooth, the morphological features and cell membrane polarization are unique among collagen-synthesizing cells [39, 205]. Odontoblasts are terminally differentiated post-mitotic cells, meaning that they have withdrawn from the cell cycle and cannot be replaced by cell division [39, 209]. Coronal odontoblasts are highly polarized both morphologically [39] and by cell membrane polarity [205] and organized in a pseudostratified palisade, while in root they form a single cell layer [39]. The cell body is located on a pulpal wall of dentin and odontoblast processes inserted into dentinal tubules (Figure 2.5). The cell body is 20–40 µm tall, depending on dentinogenic activity, and contains a large nucleus at the basal portion of the cell, Golgi apparatus, rough endoplastic reticulum, several mitochondria and other intracellular structures [39]. Adjacent odontoblasts are attached with extensive tight junctions forming a stable barrier between cell bodies but may be disrupted e.g. as a response to trauma or caries [23, 40, 209]. The cytoplasmic odontoblast process penetrates into mineralized dentin tubules. It has a 0.5–1 µm main trunk and thinner lateral branches through which the processes may be connected with each other [27, 39, 209] (Figure 2.6). The odontoblast processes are suggested to detect the integrity of the region, acting as a receptor field. Any stimulation is transmitted to the cell body, inducing responses that aim to maintain the tooth integrity. At the same time, the processes withdraw, leaving the tubules empty [127], which in ground section is seen as so-called dead tracts. The extent of odontoblast processes into dentinal tubules is still a matter of debate due to the conflicting results obtained with different research methods and by the possible species differences. In rat molars, odontoblast processes extend all the way to the DEJ [127]. In human teeth, most studies indicate that the odontoblast cell processes would not extend far from the dentin-pulp border (200–700 µm) [27, 209].

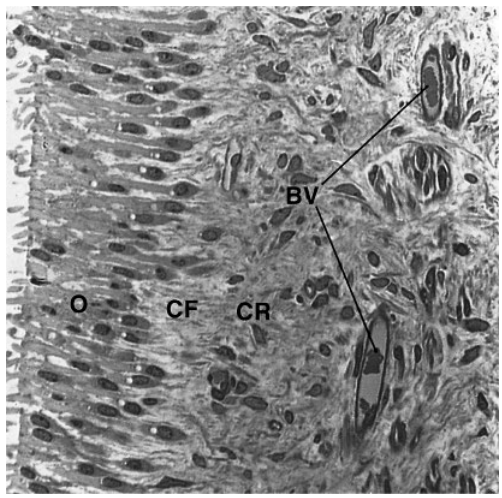


Figure 2.4 Tall, columnar odontoblasts (O), the relatively cell-free zone (CF) and the relatively cell-rich zone (CR) in the dental pulp ((BV), blood vessels).

The 10–30 µm layer of unmineralized predentin is located between odontoblasts and mineralized dentin (Figure 2.5). This is where the dentin organic matrix is organized [14] before the controlled mineralization at the mineralization front to form intertubular dentin. The backbone of the organic matrix is type I collagen, whereas non-collagenous proteins – glycoproteins, proteoglycans and enzymes – control the matrix maturation and mineralization (Figure 2.5). The mineralization

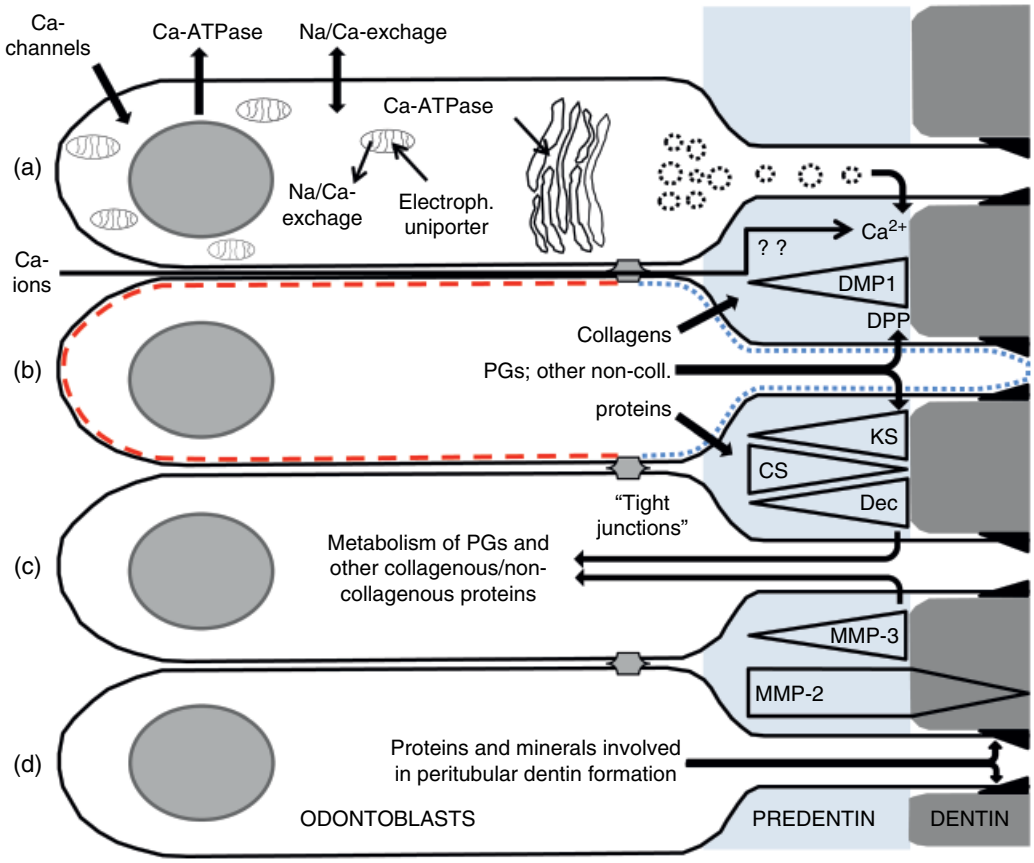


Figure 2.5 Schematic description of odontoblast function in dentin formation. Factors involved in dentin matrix formation, maturation, and mineralization. (a) Ca^{2+} ion transport and handling in the odontoblasts to provide calcium for mineralization and to maintain physiological cytosolic Ca^{2+} concentration. Intravesicular Ca-ATPase-dependent accumulation of Ca^{2+} is needed for the controlled transport in the mineralization front. Some calcium may also enter via an intercellular route despite the presence of tight junctions at least in cases of odontoblast cell layer integrity disruption (arrow with question marks). (b) Dentin organic matrix components are processed by odontoblasts and secreted into predentin at precise locations (e.g. dentin phosphoprotein, DPP, directly at or close to the mineralization front). Differential presence of Dentin matrix protein-1 (DMP1), proteoglycans (PGs, e.g. decorin [Dec]) or their side-chains (keratin sulfate [KS], chondroitin sulfate [CS]) indicate enzymatic modifications of the proteins in the predentin for controlled mineralization. Enzymes such as matrix metalloproteinases (e.g. MMP-2 and -3) participate in protein processing during predentin maturation. Cell membrane is highly polarized into basolateral process (blue dotted line) and apical cell body membrane (red dashed line), divided by tight junctions [205]. (c) Odontoblasts also have a transport system that excludes the unwanted proteins and degradation products from predentin. (d) Odontoblasts are also responsible for peritubular dentin formation. Modified from [209].

of dentinal collagen happens via proteoglycan-collagen interaction in the collagen gap zone (intrafibrillar mineralization) [43, 209]. Interestingly, matrix vesicles that are responsible for immature bone and calcifying cartilage mineralization are involved in mantle dentin and reparative dentin but not in primary or secondary dentin mineralization [193]. The mineralization front is often considered to be linear, but actually mineralized globular protrusions called calcospherites are common [209, 213].

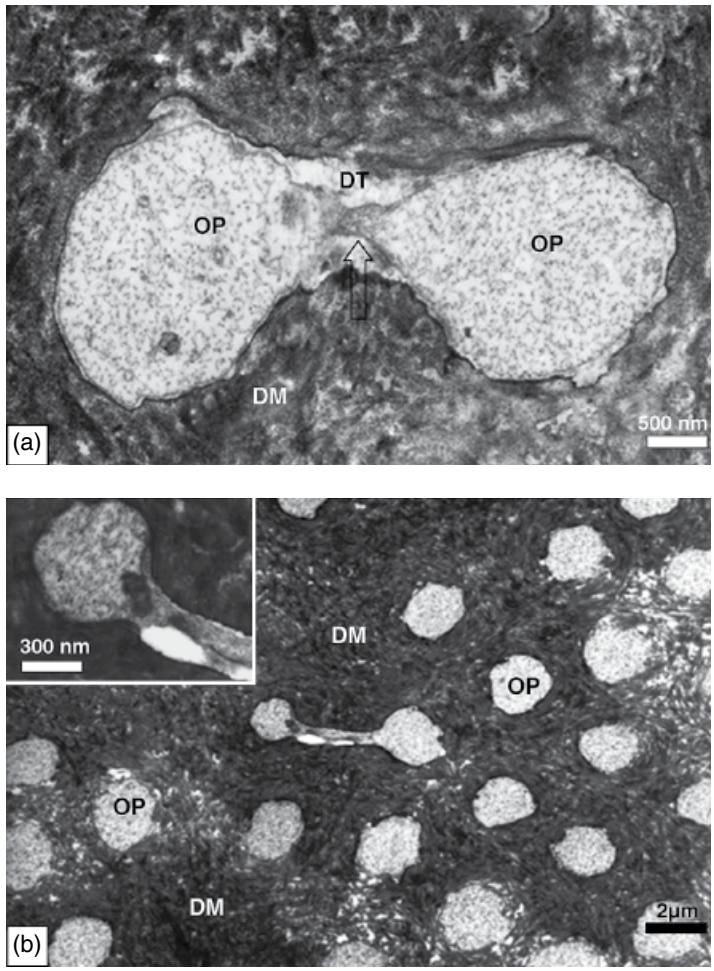


Figure 2.6 Odontoblasts processes (OP) with presence of intercellular connections (empty arrow) filling the the dentinal tubules enveloped by intertubular dentinal matrix (DM) (original magnification (a) 10,000×; (b) 2500×; inset 20,000×). (Reproduced from [27] with permission from *Tissue and Cell*.)

2.2.2 Dentin Structure

Dentin can also be divided according to the time of formation into: dentin-enamel junction (DEJ); mantle dentin; primary and secondary dentin; and tertiary dentin, which is further divided into reactionary or reparative dentin, according to the structure and the cells responsible for formation.

2.2.2.1 DEJ and Mantle Dentin

In humans, DEJ is a 7–15 µm wide wavy, scalloped structure [59, 131, 169, 213] that is different from both enamel and dentin [59]. The scalloped form of the interface is believed to improve the mechanical attachment of enamel to dentin. Mantle dentin is 5–30 µm thick layer of the outermost dentin. The matrix is formed during and immediately after the odontoblast terminal differentiation, contains organic remnants of dental papilla, and the mechanisms of mineralization is different from that at the mineralization front [193, 209]. Instead of large tubules, small ramifications of each tubule are present in mantle dentin (Figure 2.7). Unlike the rest of dentin, mantle dentin contains type III collagen (so-called von Korff fibers).

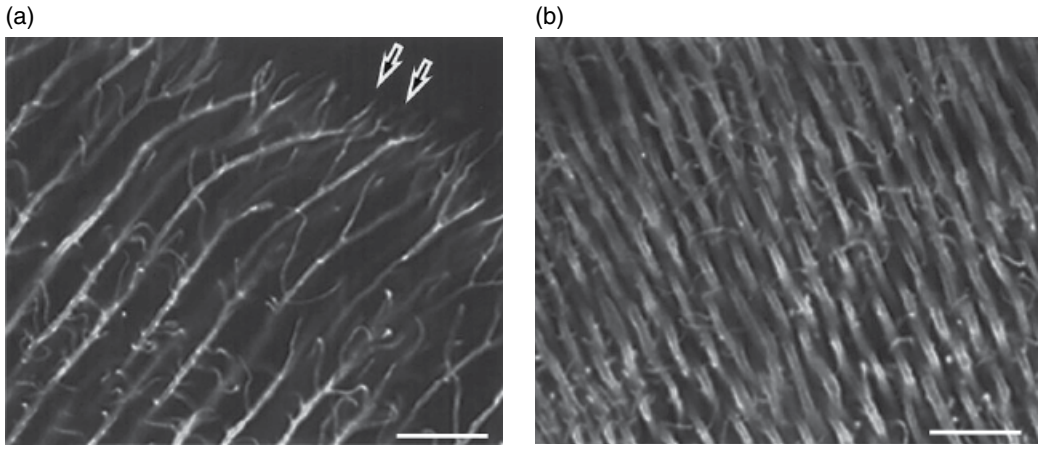


Figure 2.7 (a) Intensive branching of human tooth dentinal tubules close to DEJ (arrows). (b) Intensive branching of dentinal tubules in the middle part of dentin (bars: 20 μm). (Reproduced from [101] with permission from *Anatomy and Embryology*.)

There appears to be a gradual change of the mineralization rate from the mantle dentin towards the pulp [197], which may create up to 500 μm "resilience zone" necessary to prevent fractures under high occlusal forces [197, 208, 231, 232].

2.2.2.2 Primary and Secondary Dentin

Primary dentin formation (primary dentinogenesis) occurs during the formation and growth of the bulk of the crown and root, forming the main portion of dentin. After it, dentin formation continues as secondary dentin at approximately 1/10 of the rate [208]. The exact time for the "end" of primary dentinogenesis is vague, and actually primary dentin formation slows down gradually [100]. The difference between primary and secondary dentin even in histological or electron microscopy images is often difficult, and has no clinical relevance. Secondary dentin formation continues throughout life, leading to gradual obliteration of the pulp chamber and root canals [208].

2.2.2.3 Dentinal Tubules and Peritubular Dentin

Dentin tubularity contributes e.g. to the mechanical properties [11–13, 129] and behavior in dentin bonding [202]. Generally speaking, the tubules extend from the DEJ at right angles and run smoothly S-shaped course to the dentin-pulp border, but the direction may be different immediately beneath enamel [232]. Tubule orientation may also be different between the dental arches [232], which may affect the mechanical response to loading of teeth in occlusion [208, 232]. The density of the tubules varies depending on the location in the tooth, but is always highest in the dentin-pulp border and reduces towards the DEJ [142] (Figure 2.8). The number of tubules slowly decreases towards the apex, and in the root dentin and especially in the apical area, extensive branching occurs [77, 129, 142, 143]. In coronal area, it is highest and the direction is straighter under the cusps, where also the odontoblast processes [212, 229] and dense nerve innervation [23] penetrate deeper into the tubules. This may relate to the sensing of external irritation and contribute to the regulation of dentin-pulp complex defensive reactions.

Peritubular (intratubular) dentin forms in a regular circular manner on the walls of the dentinal tubules (Figure 2.9). This highly mineralized structure results with an age-related reduction in tubular lumen diameter, even complete occlusion of the tubule.

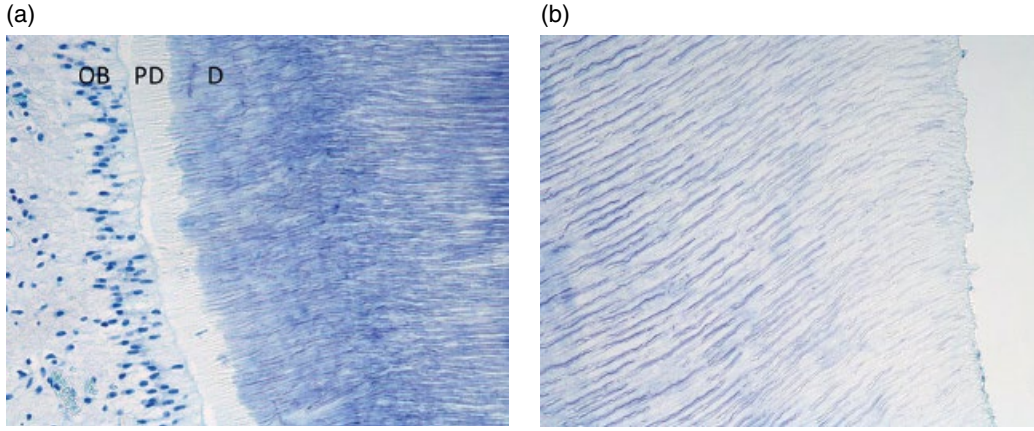


Figure 2.8 Dense tubularity close to the dentin-pulp border (a) and much sparser close to the DEJ (b). Toluidine blue staining of a human third molar from a young patient. OB: odontoblasts; PD: predentin; D: dentin.

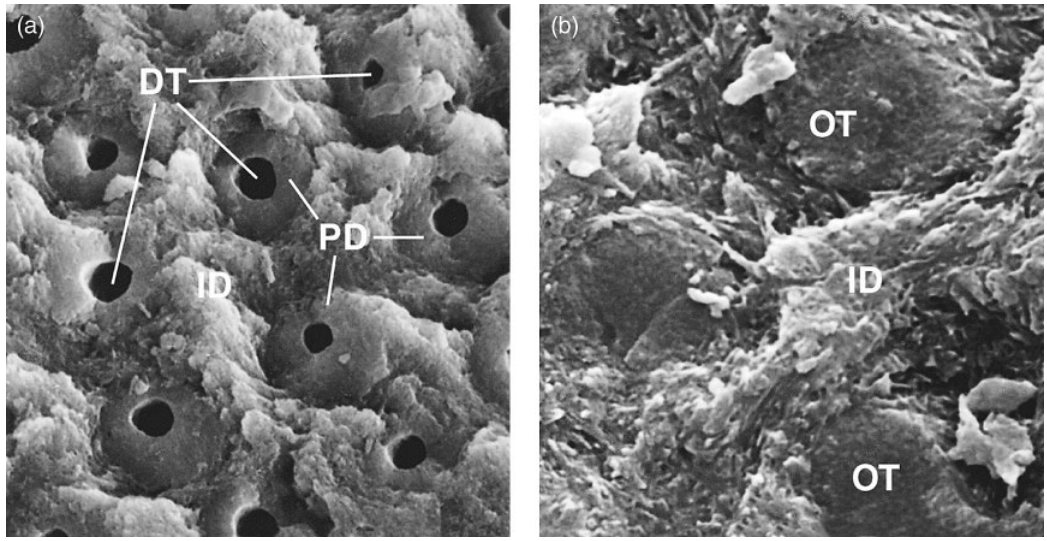


Figure 2.9 Fractured dentin showing intertubular dentin (ID), peritubular dentin (PD) and dentinal tubules (DT): (a) newly erupted tooth; (b) obturated dentinal tubules (OT) in a tooth from an old individual.

This is called dentin sclerosis. The tubules may also be occluded by mineral crystals due to reprecipitation or from the mineral ions from the dentinal fluid in cases of extensive wear or caries. Often this phenomenon is also called dentin sclerosis, although "reactive (dentin) sclerosis" would be a more appropriate term [208]. Peritubular dentin is often heterogeneous, and it is perforated by tubular branches and several small fenestrations [70], which allow dentinal fluid and its components to pass across the peritubular dentin.

2.2.2.4 Tertiary Dentin

Tertiary dentin is formed as a response to external irritation, including physiological and pathological wear and erosion, trauma, caries (in case of which both the lesion size and activity may affect [16]) and cavity preparation, and chemical irritation. The growth factors and other bioactive molecules

present in mineralized dentin and liberated during caries or wear are believed to initiate and control the tertiary dentin formation and structure [187]. Tertiary dentin increases the mineralized barrier thickness between oral microbes and other irritants and pulp tissue, aiming to retain the pulp tissue vital and non-infected. The form and regularity of tertiary dentin depends on the intensity and duration of the stimulus. There are two kinds of tertiary dentin: reactionary dentin, formed by original odontoblasts, and reparative dentin, formed by newly differentiated replacement odontoblasts [16, 138, 171, 173, 209] (Figure 2.10). Reactionary dentin is tubular and relatively similar to secondary dentin in structure, while reparative dentin (also called fibrodentin or even "calcified scar tissue" [16, 138, 171, 209]) is usually atubular or poorly tubularized and may present in variable forms (Figure 2.11). Reparative dentin is believed to be relatively impermeable, forming a barrier between tubular dentin and pulp tissue.

2.2.2.5 Root Dentin

Root dentin bears some distinct differences to coronal dentin. Right under cement, the granular layer of Tomes represents coronal mantle dentin with thin canaliculi and poorly fused globules. The granules contain uncalcified or poorly calcified collagen fiber bundles, and has been suggested to function as a "resilience zone" similar to mantle dentin [102]. As mentioned above, tubular density in root dentin is lower than in coronal dentin, especially in the most apical part [77, 129, 142, 143] (Figure 2.12). Age-related root tubular sclerosis starts from the apical region and advances coronally [149, 216], influencing root dentin permeability [164, 198]. Also, other regional differences occur, as buccal and lingual root canal dentin has patent tubules, while the mesial and distal dentin can be completely occluded [164, 198] (Figure 2.13). These tubular patency/occlusion patterns may correspond to stress distributions under occlusal loading [208], and affect both the bacterial penetration and disinfection [164, 198].

The apical part has also relatively large number of accessory root canals and apical branching (apical delta) and cementum-like lining the apical root canal wall [208] (Figure 2.14). The percentage of apical delta varies between 5.7% (maxillary anterior teeth) to 16.5% (mandibular molars), with the average number of canals being 4 (range 3–18) and about 87% having vertical

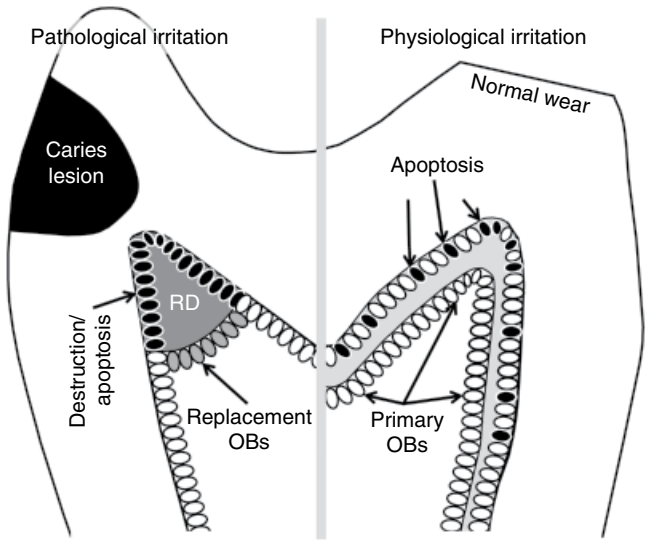


Figure 2.10 Intensive irritation (e.g. deep caries lesion) induces local odontoblast destruction and apoptosis and differentiation of replacement odontoblasts forming reparative dentin (RD). Normal wear or other mild irritation induces reactionary dentin formation by primary odontoblasts. Crowding of the odontoblasts causes apoptosis of selected cells (black cells). Modified from [209].

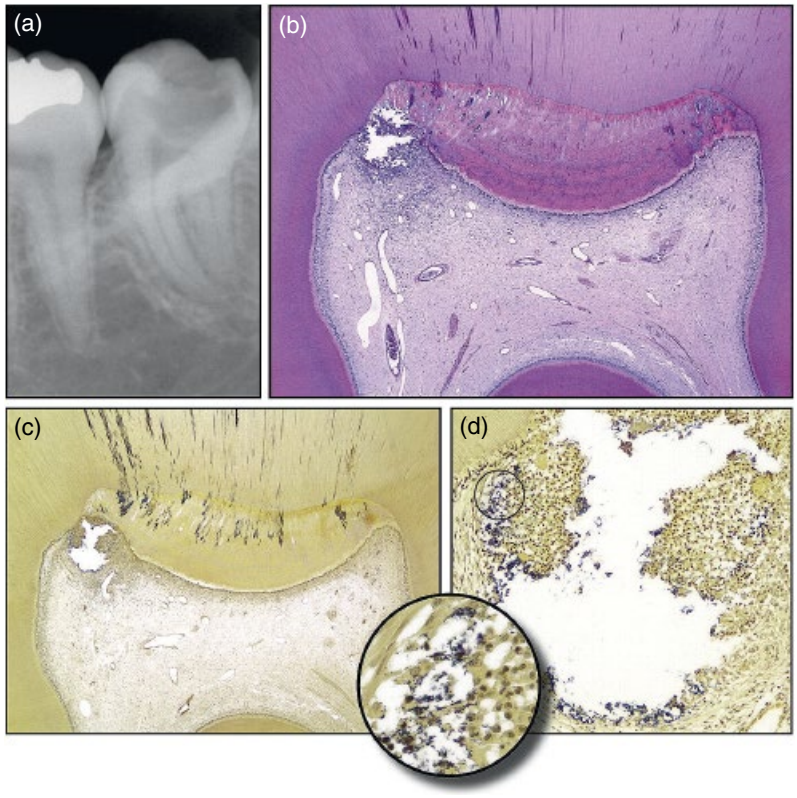


Figure 2.11 (a) A radiograph of a lower molar tooth with deep occlusal caries. (b) Tertiary dentin, consisting of both reactionary and reparative type. A limited area of necrosis is present in the mesial pulp horn (hematoxylin-eosin, original magnification 16×). (c) A section close to that in B (Taylor's modified Brown and Brenn, original magnification 16×). (d) A detailed view of the local microabscess. Bacteria surrounded by inflammatory PMNs on the right, fibroblasts on the left (original magnification 100×; inset 400×). (Reproduced from [172] with permission from *Journal of Endodontics*.)

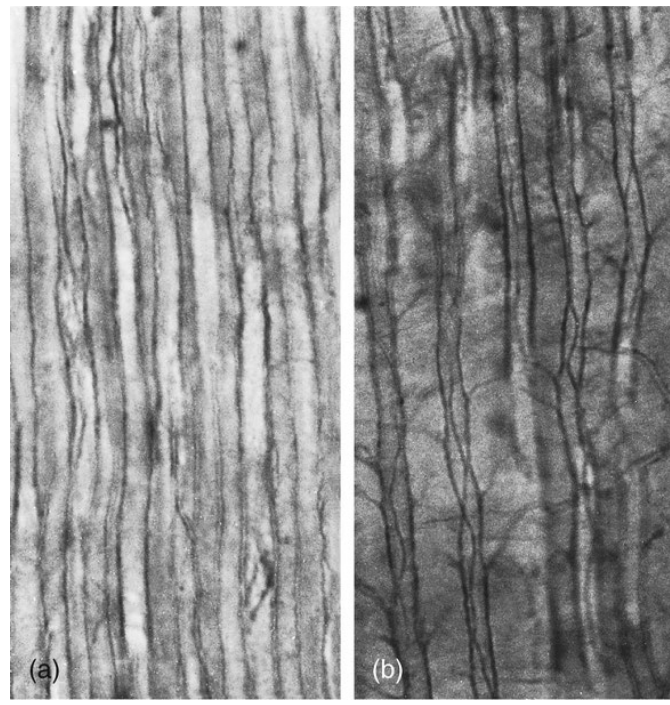


Figure 2.12 Longitudinal view of dentinal tubules: (a) in the crown; (b) in the root. The tubules are further apart in the root than in the crown and numerous fine branches are found in the root. Hematoxylin and eosin stained sections.

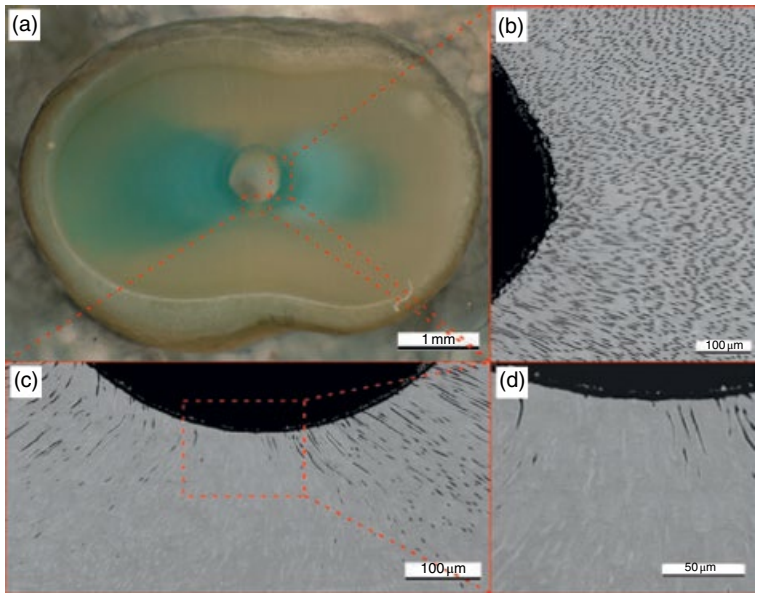


Figure 2.13 Cross-section of a tooth showing the typical bucco-lingual dye penetration (a). (b–d) Backscattered electron micrograph of areas with (b) and without (c, d) dye penetration. Patent dentinal tubules in dye-penetrated area and marked tubular sclerosis in approximal, non-dyed areas (c, d). Original magnifications: (a) 16×; (b), (c) 1000×; (d) 3000×. (Reproduced from [164] with permission from *Journal of Endodontics*.)

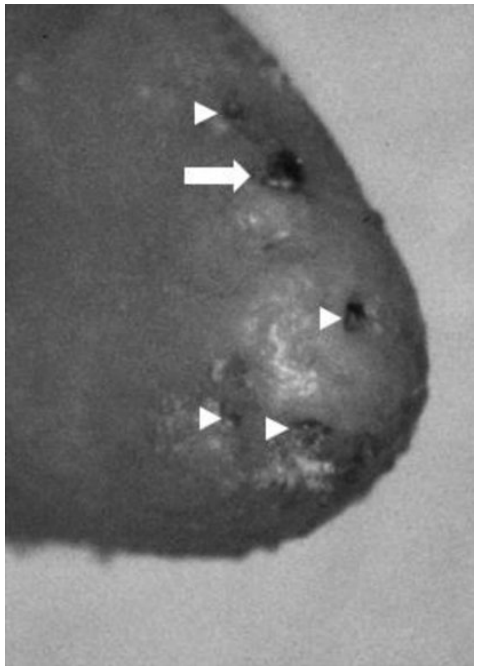
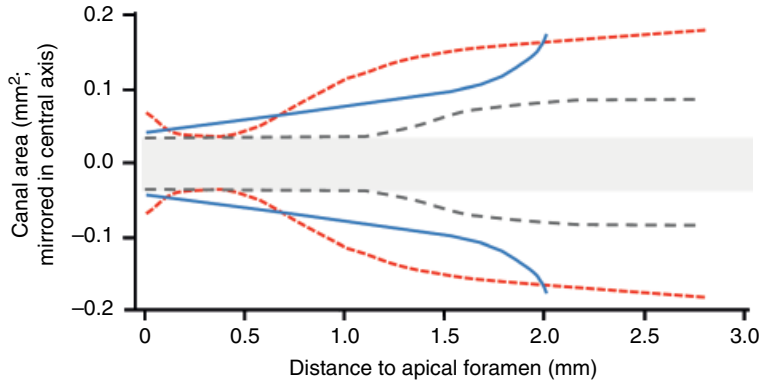


Figure 2.14 Human canine root tip with the major foramen (arrow) and four accessory foramina (arrowheads) large enough to easily fit ISO 10 instrument.

extension of 3 mm or less [60]. The traditional form of single narrow apical constrict was questioned in a recent micro-CT study, identifying long (≥ 1 mm) parallel form as the most common, and also a tapered form with no clear constrict as relatively frequent in all types of teeth [179] (Figure 2.15).

2.2.3 Dentinal Fluid

The space between the odontoblast process and tubule wall is filled with dentinal fluid. The odontoblast cell layer forms a functional barrier which mostly restrains the passage of fluid, ions and other molecules along the extracellular pathway, and at least in teeth without tissue damage (e.g. caries, cavity preparation, abrasion), dentinal fluid content is believed to be strictly under odontoblast control [209] (Figure 2.5). Dentin also contains several serum proteins, at least albumin, IgG, transferrin, fetuin-A and superoxide dismutase 3 (SOD3) [135], believed to be present mainly in dentinal tubules. With the exception of



Legend	Shape	Anterior	Premolar	Molar
	Traditional	20 (7–46)	6 (1–24)	14 (6–30)
	Taper	12 (3–37)	8 (2–28)	12 (5–28)
	Parallel	68 (43–86)	86 (65–95)	74 (57–86)

Figure 2.15 Cross-sectional apical root canal areas with different forms of the apical constriction, and the distribution (percentage with 95% confidence intervals) in different tooth groups. Each point represents a canal cross-section. X-axis: distance to apical foramen in mm, Y-axis: canal area in mm^2, mirrored at the zero axis. Modified from [179].

transferrin [160] they are not expressed by the odontoblasts. Therefore, serum proteins have a passage to dentinal fluid, even in intact teeth. However, the presence of SOD3 [165] and even 100 to 200-fold higher concentration of fetuin-A in dentin compared to serum [200] strongly indicate active transport systems by the odontoblasts [209].

Some evidence exists that physiological dentinal fluid flow may be controlled by endocrine system. A factor called parotid hormone is suggested to affect dentinal fluid flow rate. This hormone, secreted under hypothalamus control has been isolated from bovine, rat and porcine parotid glands and is present in plasma [175, 209]. A synthetic parotid hormone has equal biological activity to respective parotid gland-purified hormone in enhancing intradentinal fluid movement [233].

Dentinal fluid has a distinct role on the stress-strain distribution within the bulk dentin, increasing resilience (the capacity to absorb energy elastically upon loading) and toughness (the ability to resist fracture) [109]. In carious teeth, dentinal fluid is considered a protective factor through the occlusion of dentinal tubules (especially in slowly progressing, chronic lesions) [141] and as part of the innate response of the dentin-pulp complex with the deposition of intratubular immunoglobulins [73]. Both the quality and the quantity of immunoglobulins seem to vary according to caries depth and intensity even in uninfected tubules [73]. However, it is important to realize that inward flow also occurs all the way to the pulp [23, 117] even through enamel, at least in young teeth [23]. The study with different size microspheres demonstrated the size-dependence of penetration, the larger ones (0.2–1 µm, the size of small microbes) in the inner third of dentin and the smallest (0.02–0.04 µm) even in the pulp [117]. Thus, outward fluid flow is not capable of "washing out" the noxious stimuli from the tubules. Dentinal fluid also affects the success of adhesive restorative procedures. Increased dentinal wetness, due to increased size of dentinal tubules and fluid flow, makes successful bonding in deep cavities (close to pulp) more difficult

than to superficial dentin [166]. Dentinal fluid may cause degradation of hydrophilic adhesives, but also increase the collagen degradation rate in the hybrid layer, both leading to decrease in bond strength durability [202].

2.3 Pulp Tissue and its Homeostasis

The pulp tissue – sometimes called pulp proper – is loose connective tissue with type I and III collagens. Cells and structures are embedded in a gelatinous ground substance, containing mainly of chondroitin sulfates, hyaluronates and proteoglycans and interstitial fluid. The cells depend on the interstitial fluid as a mean for nutrient and oxygen transportation and elimination of metabolic waste products (Figure 2.16). Nerves and blood vessels enter the pulp through the apical foramen or foramina (Figure 2.17). They run close together until the main branching takes place in the coronal pulp and final, profuse branching in the odontoblast/sub-odontoblast region (Figure 2.18).

2.3.1 Pulp Cells

The main cell population in the pulp tissue are fibroblasts. Immediately under the odontoblast layer there is relatively cell-free layer (of Weil) rich in tenascin and fibronectin but low amounts of type III collagen [134]. Below that is the cell-rich layer with dense population of fibroblasts (Figure 2.4). The distribution of the fibroblasts in the rest of the pulp is less dense and relatively uniform. The pulp also contains mesenchymal stem cell-like dental stem cells with self-renewal capacity and multidifferentiation potential [18]. Pericytes are perivascular stellate cells forming a discontinuous layer in close contact with the endothelial cells surrounding capillaries and a continuous layer around microvessels [176]. They are classically considered as regulators of angiogenesis and blood pressure. Nowadays, pericytes (or their precursors) are recognized to have mesenchymal stem cell characteristics,

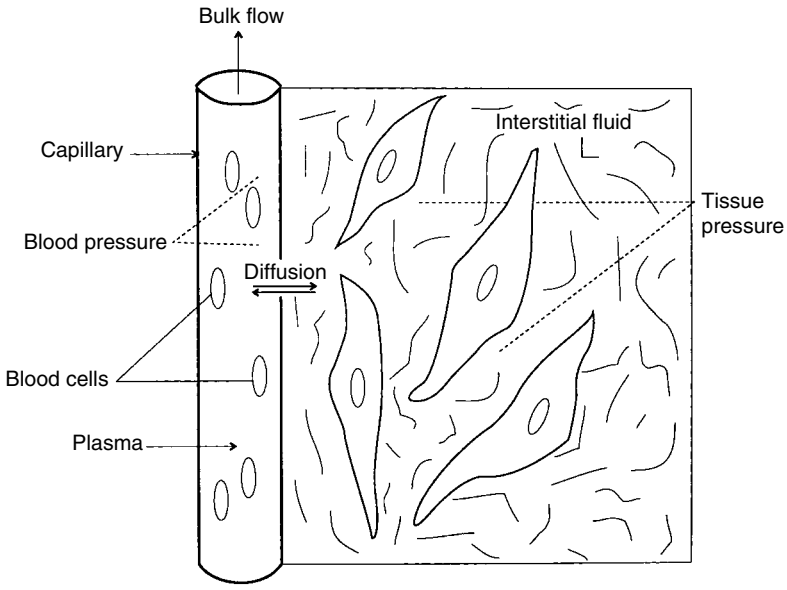


Figure 2.16 Schematic diagram illustrating capillary, cells and interstitial fluid. Blood is brought to the capillaries by bulk flow, and diffusion links plasma and interstitial fluid. The cells are surrounded by interstitial fluid acting as an extension of the plasma.

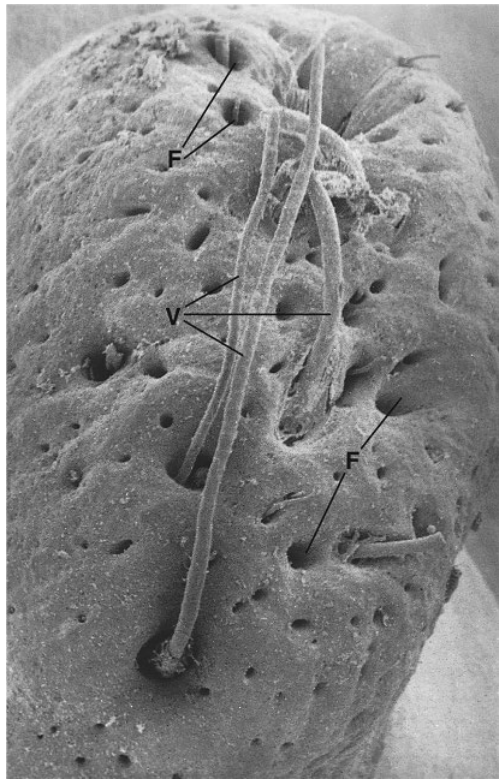


Figure 2.17 Vessels (V) entering/leaving the pulp through numerous apical foramina (F) in a dog tooth. The number of foramina is not representative for human teeth. (Reproduced from [192] with permission from *Journal of Endodontics*.)

including multipotentiality. They are selectively capable of differentiating into adipocytes and hard-tissue-forming cells osteoblasts and chondrocytes [95, 176] also in dental pulp [162, 230], possibly along with other mesenchymal stem cells of a nonpericyte origin [55].

2.3.2 Blood and Lymph Vessels

Like in any tissues, blood flow is required in the pulp to bring oxygen and nutrients to the cells, and to remove carbon dioxide and metabolic waste products. The pulp circulation is supplied by the maxillary artery, dividing into dental arteries and further arterioles that enter the teeth via apical foramina and through lateral canals. Arterioles are centrally located, and some of them pass directly to the coronal pulp while others supply the root pulp. The blood drains into venules, which largely follow the same course as the arterioles and a triad of arteriole, venule and nerve is often found in central pulp (Figure 2.19). The vasculature differs between the crown and the root. In the root, blood vessels penetrate the apical area of the pulp and form tiny branches. In crown area, capillaries form a subodontoblastic plexus of successive individual glomerular structures that each supply 100–150 µm of subodontoblastic and odontoblastic

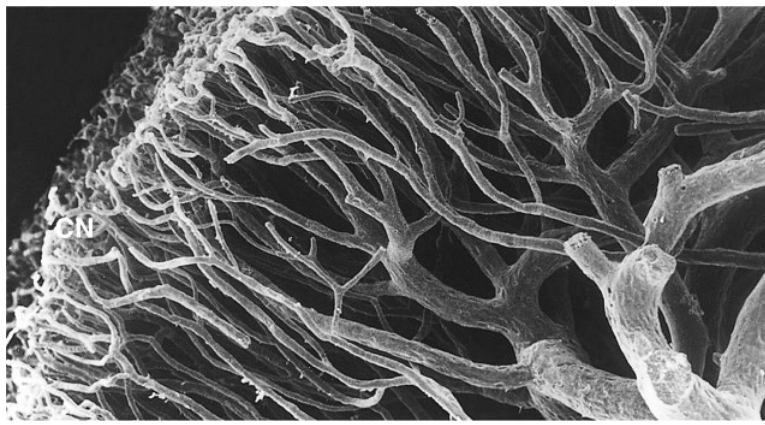


Figure 2.18 Blood vessels in the pulp. Note terminal capillary network (CN) subjacent to the predentin. (Reproduced from [192] with permission from *Journal of Endodontics*.)

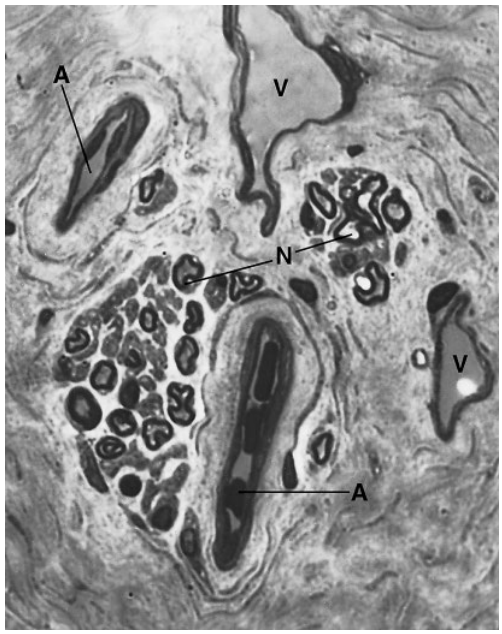


Figure 2.19 Area from the central part of the pulp showing the triad arteriole (A), venule (V) and nerve (N).

areas [90]. In young teeth with rapid dentinogenesis, capillaries enter the odontoblast cell layer to ensure their nutrition. Pulp capillaries are relatively thin-walled, may be discontinuous and fenestrated [28, 52, 90]. Pericytes are embedded within the capillary basement membrane, where they may migrate and undergo transition to a fibroblastic phenotype [28], modulate inflammatory events (e.g. leakage of plasma proteins) and may be involved with calcification of blood vessels [186] and thus be related to pulp stone formation. The blood vessels of pulp are innervated by sensory and by sympathetic nerve fibers (Figure 2.20) [23, 81].

The pulp tissue interstitial fluid has lower colloidal osmotic pressure than blood plasma, favoring capillary absorption. This helps to retain low tissue pressure, which is essential for the proper function of the blood vessels in the dentin-encased low-compliance environment. Surprisingly, the presence of lymphatics in dental pulp still remains controversial. The

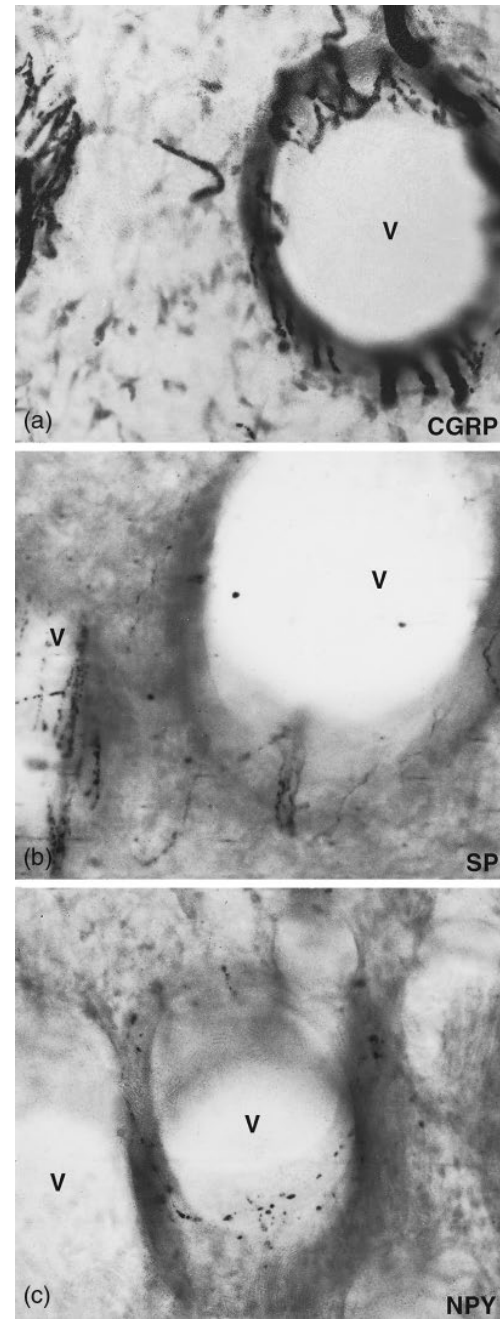


Figure 2.20 Serial cross-sections of vessels (V) from cat canine pulp. Network of sensory nerve fibers containing the neuropeptides CGRP (a), substance P (b) and neuropeptide Y (c) in the vessel walls. (Reproduced from [81] with permission from *Acta Odontologica Scandinavica*.)

earlier studies indicating pulp lymphatic capillaries have lately been disputed especially in studies using specific lymphatic markers [64, 119, 133, 218].

2.3.3 Nerves

Both myelinated and unmyelinated nerves are present in the pulp (Figure 2.21), majority of them being sensory. The sensory innervation of the pulp is very effective, terminating mostly in the odontoblast layer, predentin, and inner 0.1 mm of mineralized coronal dentin, where they run in close proximity of the odontoblast processes [27, 41] (Figure 2.22). There are at least six dental sensory nerve fiber types with specific distribution to focus on particular regions of blood vessels, coronal pulp, and dentin (Table 2.1). The sensory fibers are especially dense near the pulp horn tips, where sensitivity is also greatest, and gradually decrease towards the dentin-enamel junction (DEJ). Only few nerve endings are present in root pulp and

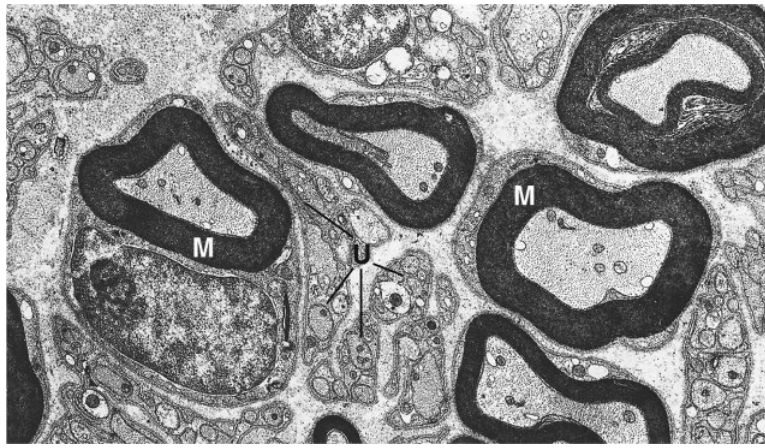


Figure 2.21 Electron micrograph illustrating details of a nerve from the central part of a pulp with myelinated (M) and unmyelineated (U) nerve fibers. (Reproduced from [41] with permission from *Acta Odontologica Scandinavica*.)

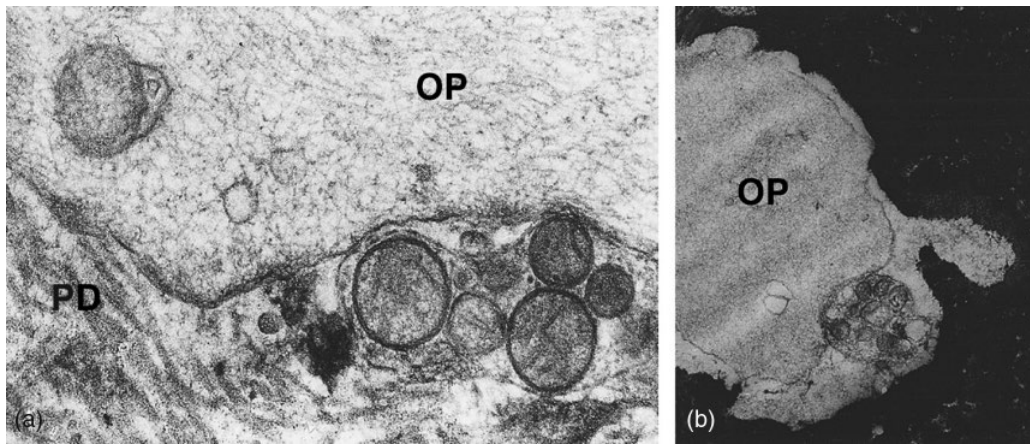


Figure 2.22 Nerve fibers in the periodontoblastic space (a) in the predentin (PD) and (b) in dentin and close contact with the odontoblast processes (OP). (Reproduced from [41] with permission from *Acta Odontologica Scandinavica*).

Table 2.1 The types, roles, mechanisms of activation, and sites of terminal endings of pulpal nerves.

Fiber type	Sensation	Activation	Terminal sites
Sensory			
A-beta	"Prepain", sharp pain	Mechanical: vibration, dentin fluid movement Electric (low voltage) Chemical: mustard oil, serotonin	Primary: Predentin, OBs, Secondary: dentin, pulp
A-delta fast	"Prepain", sharp pain	Intense cold Mechanical: dentin fluid movement Electric (mid-voltage) Chemical: mustard oil, serotonin	Primary: dentin, predentin, OBs Secondary: pulp
A-delta slow	Ache	Intense cold Electric (high voltage) Pulp damage (ATP) Chemical: capsaisin	Primary: pulp Secondary: blood vessels
C-fiber – polymodal	Ache	Intense heat Electric (high voltage) Pulp damage (ATP)	Primary: pulp Secondary: blood vessels
C-fiber – silent	Ache	Chemical: capsaisin, histamine, bradykinin	Primary: pulp Secondary: blood vessels
C-fibers	Ache	Electric (high voltage) Tissue damage (?)	Primary: OBs, pulp, blood vessels
Sympathetic			
C-fiber		Sympathetic activation, inflammatory mediators	Primary: blood vessels, pulp

dentin-pulp border [23]. Pulp innervation is closely related to the microvasculature [90] where the blood vessels are innervated by sensory and by sympathetic fibers, and a few other sympathetic fibers are located in cervical pulp [23, 90]. Nociceptive nerve fibers alert of damage and cause reflex withdrawal that limits the intensity of the initial injury. They also facilitate repair via amplifications of inflammatory, immune and healing mechanisms. Pulpal peripheral nerve fibers secrete a variety neuropeptides that activate receptors on the plasma membrane on target cells and affect tissue homeostasis, blood flow, immune cell function, inflammation, and healing. This phenomenon is called neurogenic inflammation, and occurs in the absence of direct chemical, thermal or microbial irritation [19, 23, 30]. Nerve fibers also adjust their own functions, cytochemistry, and structure to fit the tissue conditions [23, 65]. On the other hand, adrenergic agonists – better known for their vasoconstriction effect – may directly inhibit of dental nociceptor afferents [31, 76] and environmental conditions, such as pH, can regulate the nociceptive afferent activity, and may be significant in the clinical development and amelioration of dental pain [69]. These examples demonstrate bi-directional tissue-nerve interactions and neuroplasticity especially prominent in nociceptive sensory fibers, the major component of dental innervation (Figure 2.20) [23].

2.3.4 Pulp Stones

Pulp stones are discrete or diffuse pulp calcifications. One tooth may contain one or several pulp stones with varying size in coronal or in radicular pulp. The exact cause of pulp calcifications remains largely unknown.

External irritation (caries, attrition) certainly may induce pulpal calcifications, but pulp stones also appear in teeth with no apparent cause (e.g. impacted third molars). There seems to be an increase in prevalence with age, especially with the cumulative effect of external irritation [67]. The age-related pulp calcifications have been related to the blood vessels and nerve fibers. Structurally, there are "true" pulp stones, lined with odontoblasts (or rather odontoblast-like cells) and containing dentinal tubules; and "false" pulp stones, which are more or less atubular calcifications, also described as dystrophic calcification [171]. The distinction between the "true" and "false" pulp stones may be artificial, as both tubular and atubular dentin can be present in a single pulp stone (Figure 2.23). Large pulp stones in pulp chamber may obstruct the canal orifices, and in root canal they may complicate access to the apical canal [67, 208]. Apart from creating problems with endodontic procedures, pulp stones do not seem to have any other significance [67].

2.4 Pulp Inflammation

The encasement of the pulp within dentin and enamel creates a low-compliance environment that is unique in human body in terms of inflammatory tissue response. As in any other tissue, external irritation regardless of its nature (chemical, mechanical or thermal) induces a local inflammatory reaction characterized by the dilation of the vessels and decrease in the blood flow resistance (Figure 2.24). Vasodilation and the early recruitment of immune cells are mainly regulated by the sensory nerves via the release of the vasoactive neuropeptides (Table 2.1; Figure 2.25) [30]. The pertinent role of sensory nerves was demonstrated in studies where denervation caused a significant reduction of immunocompetent cells [57] and dramatically advanced pulp necrosis [24] after pulp exposure. Vasodilation together with lower resistance cause an increase in intravascular pressure and capillary blood flow, leading to leukocyte extravasation and filtration of the serum proteins and fluid into the tissue, mainly in the subodontoblastic area [201]. The increase in vascular permeability and accumulation of the proteins can happen quite rapidly, and it is clearly observable already four hours after the cavity preparation [201]. The vascular reactions aim to provide inflammatory cells and to eliminate microbial toxins and metabolic waste products from the area. However, if the external irritation exceed certain threshold level (e.g. continues and intensifying microbial stimuli from advancing caries lesion), it is possible that the pulpal reaction does not limit to the restricted area. Because of the protein and fluid filtration and the increase in cell content, the tissue becomes edematous and tissue pressure increases. In almost all other tissues this would lead to swelling, but in a pulpal low-compliance environment the tissue pressure may increase to the level that exceeds venular pressure, causing the compression of the venules (Figure 2.24). This is followed by increased flow resistance and concomitant decrease in blood flow, because the venous drainage is impeded. The slower blood flow causes aggregation of red and other blood cells and local elevation of the blood viscosity, which further reduces blood flow. The following local hypoxia, increase in metabolic waste products and carbon dioxide, and decrease in pH lead to vasodilation of the adjacent vascular structures, thus leading to the spreading of inflammation (Figure 2.24). The local inflammatory reaction will lead to local necrosis (local pulpal abscess) sometimes called necrobiosis, where part of the pulp necrotic and infected and the rest is irreversibly inflamed [2, 115] (Figure 2.11). Matrix metalloproteinases (MMPs), the enzymes degrading collagen and other extracellular matrix proteins and produced by odontoblasts [206, 207, 211] and especially by the inflammatory cells (PMN-leukocytes, macrophages and plasma cells), aim to confine the spreading of infection. Both chemical [204] and genetic [136, 220]