Chapter 1

Apical Periodontitis: Microbial Infection and Host Responses

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1.1 Introduction

Traditionally, endodontology includes pulp and periapical biology and pathology. Clinically, however, endodontics is perceived as treatment of the root canal with files and the placement of a root filling, or treatment by surgical endodontics. The vital pulp and the treatment measures to preserve its vitality are usually considered a part of conservative dentistry, and include specific techniques in dental traumatology. In both principle and practice, the situation changes when pulp extirpation or root canal treatment is considered necessary. While the initial diagnoses and the difficulties associated with treatment may be related to the state of the pulp, the purpose of treatment is no longer the preservation of the pulp, but the prevention and elimination of infection in the root canal system. The ultimate biological aim of this treatment is *either to prevent or cure apical periodontitis* (Fig. 1.1). 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.

Research in recent decades has documented particularly the importance of microbial factors in the initiation, development and persistence of apical periodontitis [3,12,13,20,21,26,27,30,35] (Fig. 1.2). Emphasis must therefore be on the infectious etiology of apical

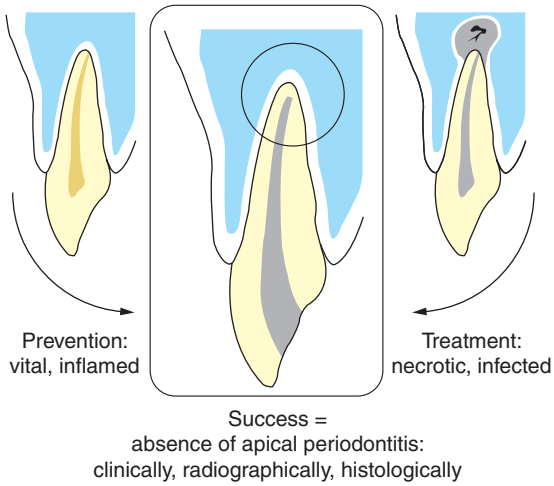

Fig. 1.1 Prevention or treatment of apical periodontitis.

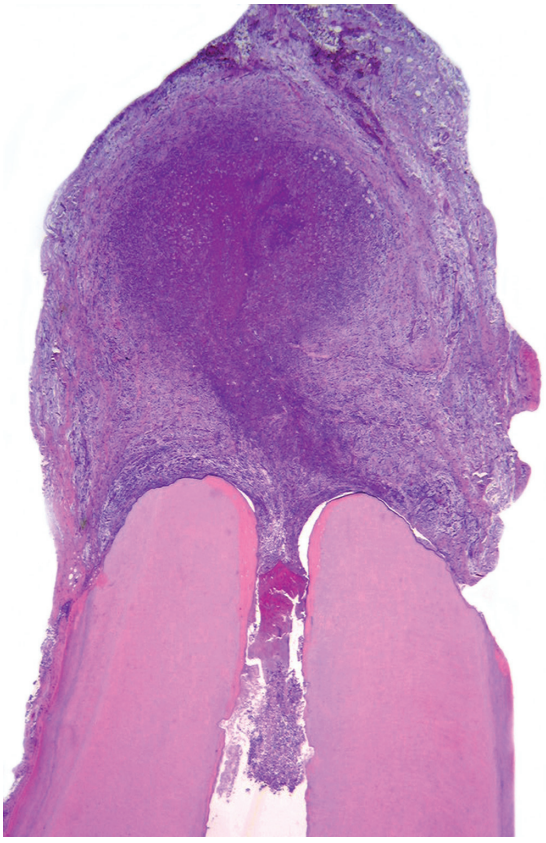

Fig. 1.2 A longitudinal section of a root with apical periodontitis. The root canal contains bacteria. (Courtesy of Dr D. Ricucci.)

periodontitis and on the importance of aseptic and antiseptic principles during treatment. Similarly, research findings have an immediate and extensive impact on aspects of diagnosis, treatment, prognosis and evaluation of outcome in endodontics. It is important to use the acquired knowledge to build treatment principles logically, and to show how these principles may and should be applied in clinical practice.

1.2 Terminology

Both pulp and pulp–periodontal diseases have been subject to almost innumerable diagnostic schemes, classification systems, and terminology. Periodontitis caused by infection of the pulp canal system has been termed apical periodontitis, apical granuloma/cyst, periapical osteitis, periradicular periodontitis, among other terms. Sub-classifications have been acute/chronic/exacerbating/Phoenix abscess, and symptomatic/asymptomatic [39]. There are arguments in favor of each of these schemes. The present text makes use of the more conservative terms, i.e., acute/chronic/exacerbating apical periodontitis as principal terminology (Table 1.1). The following is a brief argument for the retention of these terms.

Symptomatic/asymptomatic apical periodontitis has been suggested as the primary diagnostic term instead of acute/chronic apical periodontitis. This is based on the assumption that the diagnosis of chronic or acute stages of the disease is difficult or impossible when a histological definition of acute/chronic forms the reference. It is also attractive to use a terminology that may seem (relatively) unambiguous. However, as the terms chronic and acute in fact belong principally to the temporal and clinical aspects of disease, there is no basic conflict between these two schemes of classification. Furthermore, acute and chronic are generally perceived as diagnostic terms, whereas symptomatic and asymptomatic traditionally are descriptions used during history taking and examination of the patient.

Periradicular periodontitis is an alternative term that has gained increasing support [1]. Periradicular periodontitis literally means “inflammation around the tooth around the root”, and could be conceived as tautologically excessive. It includes lateral and furcal locations of inflammation, but it does not distinguish etymologically pulp-induced periodontitis from marginally derived periodontitis. “Apical” distinguishes the disease from marginally derived periodontitis, and while it does not purport to include lateral and furcal locations, these are by comparison scarce and are easily perceived as variants of their more frequent disease of reference.

Apical periodontitis includes dental abscess, granuloma and cyst as manifestations of the same basic disease; these latter terms are not in conflict with other classification schemes. The historical emphasis on the differential diagnosis of a cyst versus a granuloma may have been overstated, particularly as radiographs are poor discriminators [29]. Cysts and granulomas have the same etiology [23] (Chapters 3 and 5) and basic disease processes (Chapter 4); their treatment and prognosis are also similar (Chapters 11 and 12). However, there are studies indicating that true cysts may show impaired healing [24,26].

Table 1.1 Main terminology used in the present text

Primary term	Alternative term
Apical periodontitis	Periradicular periodontitis
Granuloma	Periapical osteitis
Cyst	
Furcal apical periodontitis	Interradicular apical periodontitis
Lateral apical periodontitis	
Acute apical periodontitis	Symptomatic apical periodontitis
	Acute apical abscess
Exacerbating apical periodontitis	Phoenix abscess
	Symptomatic apical periodontitis
Chronic apical periodontitis	Asymptomatic apical periodontitis
Apical periodontitis with sinus tract	Suppurative apical periodontitis
	Apical periodontitis with fistula
Condensing apical periodontitis	Condensing osteitis
	Periapical osteosclerosis
Transient apical periodontitis	Transient apical breakdown

The use of the term "periapical osteitis" has been limited and the connotation that bone is inflamed seems incorrect. Rather, the inflammation of the apical periodontium causes resorption of the bone and prevents it from becoming infected.

In summary, "apical periodontitis" takes preference by etymology and usage; "acute" and "chronic" are preferred and used as clinical supplementary terms of disease. On the other hand, terminology should not be used as a straightjacket for authors. Therefore, variants of the terms and references to other diagnostic schemes, in this book and other texts, are inevitable, even desirable.

1.3 Oral and dental infection

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 [5]. 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 (Fig. 1.3).

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 a consequence of the conditions within the biofilm (Chapters 4 and 5).

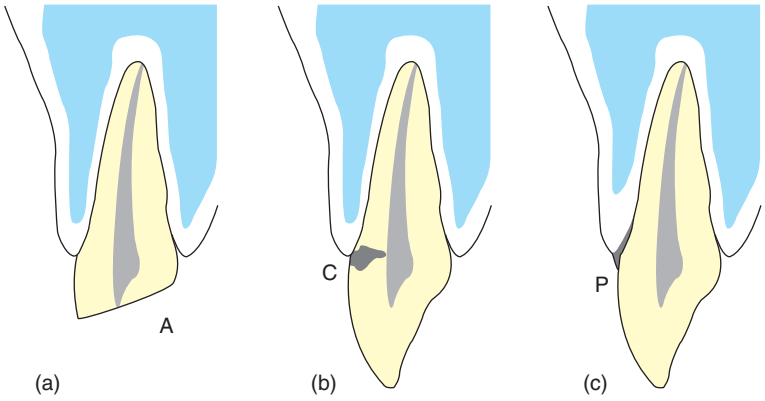

Fig. 1.3 Breaks in the mucocutaneous barrier associated with teeth. (a) Attrition (A), abrasion or trauma exposes the pulp. (b) Dental caries (C) reaches the pulp with subsequent infection of the pulp and periapical tissues. (c) Dental plaque (P) penetrates the gingival cuff and bacteria invade the gingival and periodontal tissues.

1.3.1 Marginal periodontitis

The gingival sulcus is potentially a weak link in the surface cover, combining a thin epithelial coverage with a topographic structure that favors the accumulation of bacteria on the adjoining tooth. With time, the microbial challenge in this area frequently overwhelms the body defenses and causes gingivitis and subsequent marginal periodontitis. Untreated, the ensuing inflammation is often followed by loosening of the tooth, its loss and, finally, reestablishment of the mucosal barrier. Biologically, the inflammation has a surface localization with easy drainage of pus, and deeper infection of tissues is not often seen. Moreover, tooth loss from marginal periodontitis usually happens late in the lifecycle of the individual, with limited consequences for the survivability of the individual, group or species.

1.3.2 Dental caries

Clinical dentistry and dental science have emerged in response largely to the other major, visible infection of the oral cavity: dental caries. The disease has primarily, but not exclusively, affected children and young adults; and the pain, impaired appearance, and tooth loss at an early age associated with dental caries have made it a major challenge to societies where it has become widespread. However, the epidemic of dental caries may have had a relatively short history in the lifespan of man. Although the history of dental caries goes back to the Iron Age and earlier, archaeological material and historical sources do not indicate that dental caries was widespread until a few centuries ago. Greater use of preventive measures in developed countries has caused a downturn in disease, although it still constitutes a significant health concern for some population groups and individuals.

1.3.3 Pulp infection and periapical inflammation

Infection and inflammation of the pulp and periapical tissues have long been regarded as an extension of the dental caries process. This has been a reasonable interpretation in view of the dominance of caries as a source of infection of dentin during the last few cen-

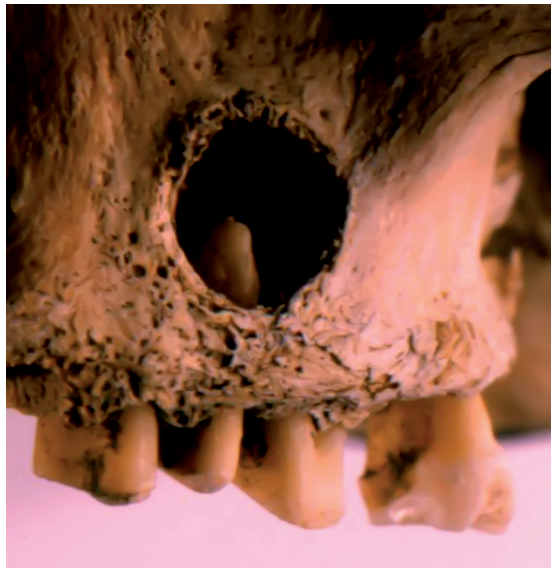

Fig. 1.4 Apical periodontitis in an upper premolar of a woman's skull found in Iceland and dating to the twelfth century. Trauma or wear caused exposure of the pulp with infection and lesion development.

turies. However, infection of the pulp and periapical tissues and the tissue responses are probably an older and more general biological occurrence than dental caries (Fig. 1.4). Despite the common origin of infecting organisms, the microbial floras of dental caries and endodontic infections differ in many respects. The evolutionary biological development of the permanent dentition, which has nonreplaceable teeth, must also have included the development of effective responses to trauma and subsequent infection of the deeper tissues.

Apical periodontitis may thus be viewed as a tissue response to pulp infection from trauma such as blows to or fracture of the teeth, attrition from mastication, and abrasion from the use of teeth as tools for survival. Essentially, apical periodontitis may be seen as the body's means of coping with the threat of infection following breaches in the mucosal/tooth barrier from trauma to, or attrition of, the teeth. An exposed pulp potentially leaves the body open to infection; the processes of apical periodontitis then usually work to create a second barrier within the body to prevent further spread of potentially threatening microbes [14,23] (Figs 1.5 and 1.6).

Treatment of apical periodontitis must be seen in the context of preventing microbial access to the jawbone and the body beyond, and needs to be achieved by effective disinfection and obturation. A complete seal from the coronal to the apical end of the treated root reestablishes the mucocutaneo-odonto barrier, whereas voids or leaks may present an opportunity for bacteria to establish a foothold close to the body's interior. The recent emphasis on coronal leakage of bacteria and bacterial products as opposed to apical leakage is a reflection of this more scientifically based line of reasoning [18,40].

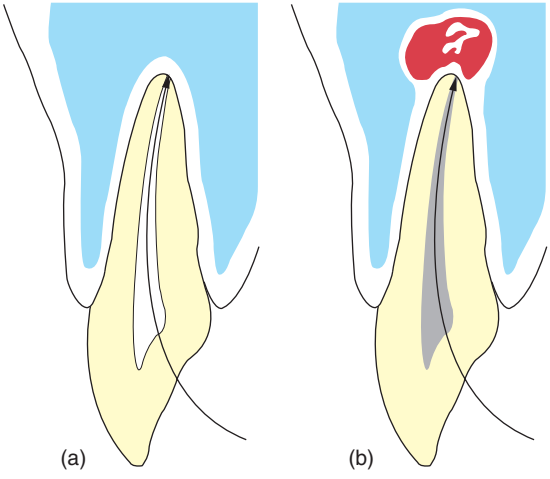

Fig. 1.5 Infection of the pulp (a) is contained by development of an apical granuloma/cyst (b).

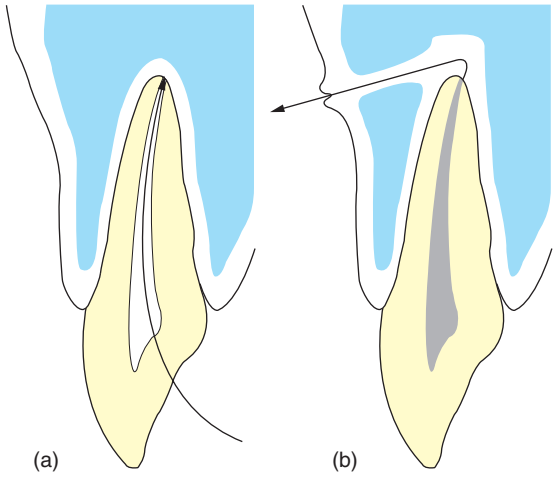

Fig. 1.6 Infection of the pulp (a) is externalized by development of a sinus tract from apical periodontitis (b).

1.4 Biological and clinical significance of apical periodontitis

1.4.1 Infection theory

In the pre-antibiotic era, infections of the pulp and periapical tissues were considered potentially serious and in need of 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 believed to be easily controllable by antibiotics. Today, it is recognized that pulp infection may be caused by organisms of different virulence [36] (Chapter 5), and that control of the infection is not always easily obtained, particularly when endodontic treatment is ineffective.

The flora of the mouth is fortunately composed of few species of pathogenic organisms, which usually have low virulence (Chapter 5). Most may be considered opportunistic, causing disease only in mixed infections or in hosts compromised by other diseases. Teleologically, it is usually not to the advantage of microbial species living on other organisms to cause disease; the basis for their presence is rather the preservation of the host.

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 in the absence of 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 [34], 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 [13].

Research has also documented that some forms of apical periodontitis may be associated with particular species dominating in the pulp canal flora (Chapter 5). Evidence from molecular analysis implies that endodontic infections may be more opportunistic than specific, and may include more species than previously thought [22] (Chapter 5). There is a need for more research into microbiological causes and interactions in apical periodontitis to improve diagnosis and treatment. Specifically, this would apply to the so-called "therapy-resistant" cases of apical periodontitis [2,7,25,42], in which infection persists despite apparently adequate root canal treatment, and to retreatment cases in which *Enterococcus faecalis* has been implicated [11].

1.4.2 Endodontic infection and general health

The focal infection theory has been a source of both frustration and inspiration in dental practice and research [6]. There has been frustration, first because irrelevant and sometimes incorrect arguments and concepts were used to dictate an unnecessary wave of tooth extractions in healthy individuals for decades; and secondly because unsubstantiated opinions on the subject for too long a time afterwards restricted clinical developments in the field of endodontics. The controversy, however, sparked important new discoveries, and it is, even today, an important part of the frame of reference that is applied to endodontic microbiology and host defense mechanisms.

Focal infection originally implied dissemination of pathogens from the focus to remote part of the body, where secondary disease arose [6]. With time, the concept was expanded to include immune products "homing" to other organs and causing disease or symptoms there. Fortunately, most, if not all, concerns of the proponents of the focal infection theory have been proven unsubstantiated. There remains, however, a recognition that apical periodontitis is a response to microbial infection that needs to be contained, cured and eliminated for optimum general health.

In view of the many patients with compromised general health who now retain their teeth into old age, it is reassuring that current research demonstrates that while bacteremias during endodontic treatment occur, the incidence or magnitude is not alarming, and indeed is comparable to, or less than, that of most routine dental procedures [9]. However, the nature of the infecting organism may possibly be a source of concern [10]. The risks of antibiotic prophylaxis need to be weighed against the consequences of bacteremia.

1.4.3 Infection control

The outcome of endodontic treatment is dependent on using an aseptic technique and antiseptic measures to eliminate infection. However, the critical role of infection control may not always be given the prominence that it deserves. The transmission of hepatitis viruses has been an issue for a long time, but there has been more recent concern about prion transmission via contaminated instruments [32]. There has been debate about reuse of root canal files from the biological perspective [17] as distinct from the mechanical perspective; protocols for instrument decontamination have been developed in the face of increasing governmental regulation.

1.4.4 Microbial specificity and host defense

The host responses to root canal infection have been the subject of much research in recent years. There is great similarity between the pathogenic processes in marginal and apical periodontitis, and many of the findings in periodontal research have direct relevance to apical periodontitis. A clearer concept of the immunological processes involved in the development of apical periodontitis is emerging [14,34] (Chapter 3). Microbiological variability and virulence factors in infected root canals have been demonstrated, and data are emerging which indicate that the bacterial flora varies systematically with the

clinical condition of the tooth involved (persistent infection, therapy-resistant infection) (Chapters 5 and 11). Thus, different strategies of antimicrobial measures may have to be applied depending on the microbiological diagnosis in a given case.

1.4.5 The compromised host

A characteristic feature of dentistry as it is practiced today is the shift of care from young to elderly people. The success of preventive dentistry in controlling and containing dental caries has resulted in a larger part of the population retaining their natural teeth longer and aspiring to keep them into old age. The improvement in dental health as regards dental caries has therefore not resulted in a decrease in demand for endodontic treatment; rather, more people in the older age groups are seeking to preserve their teeth by endodontic intervention. The net result is a stable, or increasing, demand for endodontic treatment (Chapter 8) rather than a decline. With the increased demand for endodontic care among the elderly, there is also concern for the consequences of apical periodontitis and its treatment sequels in relation to other medical conditions. Fortunately, many of the concerns which previously were held as restrictions to endodontic treatment of the elderly have not been substantiated: both the prevention and cure of apical periodontitis by endodontics seem to be as successful in the old as in the young. Moreover, initial concerns about treatment outcome in HIV-positive patients seem unfounded [28].

There are a number of medical conditions that may influence the indications for, and choice of, endodontic treatment and that occur more frequently among elderly patients. Generally, any disease for which bacteremia poses an additional hazard is of concern when endodontic treatment is being considered. Particularly, a history of infective endocarditis, congenital heart disease, rheumatic heart fever or the presence of an artificial heart valve or other susceptible implants may necessitate the implementation of an antibiotic regimen in conjunction with the endodontic procedures. The progression, possibly also prognosis and healing pattern in diabetic patients may differ from that in people not affected by the disease [16,31]. Special consideration must be given to patients who are being treated with immunosuppressants, or otherwise have compromised immune systems [37,44]. 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 [41]. A special case is presented by the irradiated patient: the high incidence of osteoradionecrosis after oral surgical procedures places high demands on effective, conservative treatment of endodontic conditions. Smoking has been shown to have an adverse effect on marginal periodontitis and wound healing; the effect of smoking on apical periodontitis has largely been overlooked, and the limited evidence is conflicting [4,19].

1.4.6 Tooth loss and replacement

Untreated apical periodontitis represents a chronic infection of the oral tissues at locations closer to more vital organs than many other oral infections. While these infections may remain quiescent for decades, they may also develop and spread with serious consequences for the individual [8,33]. 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 [43]. The variable success rates (by strict criteria) of treatment procedures for the cure of apical periodontitis [15] (Chapter 14) are sometimes put forth as arguments for the implant "treatment" concept. However, what little evidence there is does not indicate a lower survival rate of endodontically treated teeth [38], and the superiority of tooth preservation compared to its replacement should be evident as a biological principle of preference. On the other hand, the challenge from other treatment concepts to endodontics as a discipline should act as a driving force to produce more and scientifically solid evidence for the modalities of cure and prevention applied to our disease of interest, apical periodontitis.

1.5 Conclusion

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. Despite

recent technological advances in treatment, evidence of improved outcome is still lacking. Alternative treatment involving implants is promoted as being better, but the criteria of evaluation of the outcome of the two forms of treatment are dissimilar; there is no true evidence-based comparison.

1.6 References

1. American Association of Endodontists (2003) *Glossary of endodontic terms*, 7th edn. Chicago, IL: American Association of Endodontists.
2. Barnard D, Davies J, Figdor D (1996) Susceptibility of *Actinomyces israelii* to antibiotics, sodium hypochlorite and calcium hydroxide. *International Endodontic Journal* **29**, 320–6.
3. Bergenholtz G (1974) Micro-organisms from necrotic pulp of traumatized teeth. *Odontologisk Revy* **25**, 347–58.
4. Bergström J, Babcan J, Eliasson S (2004) Tobacco smoking and dental periapical condition. *European Journal of Oral Science* **112**, 115–20.
5. Bernard C (1927) *An introduction to the study of experimental medicine, 1865*. English translation by Henry Copley Greene, Macmillan & Co., 1927.
6. Billings F (1913) Chronic focal infection as a causative factor in chronic arthritis. *Journal of the American Medical Association* **61**, 819–23.
7. Byström A, Claeson R, Sundqvist G (1985) The antibacterial effect of camphorated paramonochlorophenol, camphorated phenol and calcium hydroxide in the treatment of infected root canals. *Endodontics and Dental Traumatology* **1**, 170–5.
8. Caruso PA, Watkins LM, Suwansaard P, Yamamoto M, Durand ML, Romo LV, Rincon SP, Curtin HD (2006) Odontogenic orbital inflammation: clinical and CT findings – initial observations. *Radiology* **239**, 187–94.
9. Debelian GJ, Olsen I, Tronstad L (1994) Systemic diseases caused by oral microorganisms. *Endodontics and Dental Traumatology* **10**, 57–65.
10. Debelian GJ, Olsen I, Tronstad L (1995) Bacteremia in conjunction with endodontic therapy. *Endodontics and Dental Traumatology* **11**, 142–9.
11. Evans M, Davies JK, Sundqvist G, Figdor D (2002) Mechanisms involved in the resistance of *Enterococcus faecalis* to calcium hydroxide. *International Endodontic Journal* **35**, 221–8.
12. Fabricius L, Dahlén G, Holm SE, Möller ÅJR (1982) Influence of combinations of oral bacteria on periapical tissues of monkeys. *Scandinavian Journal of Dental Research* **90**, 200–6.
13. Fabricius L, Dahlén G, Öhman AE, Möller ÅJR (1982) Predominant indigenous oral bacteria isolated from infected root canals after varied time of closure. *Scandinavian Journal of Dental Research* **90**, 134–44.
14. Kawashima N, Okiji T, Kosaka T, Suda H (1996) Kinetics of macrophages and lymphoid cells during the development of experimentally induced periapical lesions in rat molars: a quantitative immunohistochemical study. *Journal of Endodontics* **22**, 311–16.
15. Kirkevang LL, Vaeth M, Hörsted-Bindslev P, Wenzel A (2006) Longitudinal study of periapical and endodontic status in a Danish population. *International Endodontic Journal* **39**, 100–7.
16. Kohsaka T, Kumazawa M, Yamasaki M, Nakamura H (1996) Periapical lesions in rats with streptozotocin-induced diabetes. *Journal of Endodontics* **22**, 418–21.
17. Linsuwanont P, Parashos P, Messer HH (2004) Cleaning of rotary nickel-titanium endodontic instruments. *International Endodontic Journal* **37**, 19–28.
18. Madison S, Wilcox LR (1988) An evaluation of coronal microleakage in endodontically treated teeth. III. In vivo study. *Journal of Endodontics* **14**, 455–8.
19. Marending M, Peters OA, Zehnder M (2005). Factors affecting the outcome of orthograde root canal therapy in a general dentistry hospital practice. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **99**, 119–24.
20. Möller ÅJR, Fabricius L, Dahlén G, Öhman AE, Heyden G (1981) Influence on periapical tissues of indigenous oral bacteria and necrotic pulp tissue in monkeys. *Scandinavian Journal of Dental Research* **89**, 475–84.
21. Molven O, Olsen I, Kerekes K (1991) Scanning electron microscopy of bacteria in the apical part of root canals in permanent teeth with periapical lesions. *Endodontics and Dental Traumatology* **7**, 226–9.
22. Munson MA, Pitt Ford T, Chong B, Weightman A, Wade WG (2002) Molecular and cultural analysis of the microflora associated with endodontic infections. *Journal of Dental Research* **81**, 761–6.
23. Nair PN (2004) Pathogenesis of apical periodontitis and the causes of endodontic failures. *Critical Reviews in Oral Biology and Medicine* **15**, 348–81.
24. Nair PNR, Pajarola G, Schroeder HE (1996) Types and incidence of human periapical lesions obtained with extracted teeth. *Oral Surgery, Oral Medicine, Oral Pathology* **81**, 93–102.
25. Nair PNR, Sjögren U, Kahnberg KE, Sundqvist G (1990) Intraradicular bacteria and fungi in root-filled asymptomatic human teeth with therapy-resistant periapical lesions: a long-term light and electron microscopic follow-up study. *Journal of Endodontics* **16**, 580–88.
26. Nair PNR, Sjögren U, Schumacher E, Sundqvist G (1993) Radicular cyst affecting a root-filled human tooth: a long-term post-treatment follow-up. *International Endodontic Journal* **26**, 225–33.
27. Nair R (1987) Light and electron microscopic studies of root canal flora and periapical lesions. *Journal of Endodontics* **13**, 29–39.
28. Quesnell BT, Alves M, Hawkinson RW Jr, Johnson BR, Wenckus CS, BeGole EA (2005) The effect of human immunodeficiency virus on endodontic treatment outcome. *Journal of Endodontics* **31**, 633–6.
29. Ricucci D, Mannocci F, Pitt Ford TR (2006) A study of periapical lesions correlating the presence of a radiopaque lamina with histological findings. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **101**, 389–94.
30. Ricucci D, Pascon EA, Pitt Ford TR, Langeland K (2006) Epithelium and bacteria in periapical lesions.

Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics **101**, 239–49.
31. Segura-Egea JJ, Jimenez-Pinzon A, Rios-Santos JV, Velasco-Ortega E, Cisneros-Cabello R, Poyato-Ferrera M (2005) High prevalence of apical periodontitis amongst type 2 diabetic patients. *International Endodontic Journal* **38**, 564–9.
32. Smith AJ, Bagg J, Ironside JW, Will RG, Scully C (2003) Prions and the oral cavity. *Journal of Dental Research* **82**, 769–75.
33. Stalfors J, Adielsson A, Ebenfelt A, Nethander G, Westin T (2004) Deep neck space infections remain a surgical challenge. A study of 72 patients. *Acta Otolaryngol* **124**, 1191–6.
34. Stashenko P, Wang CY, Tani-Ishii N, Yu SM (1994) Pathogenesis of induced rat periapical lesions. *Oral Surgery, Oral Medicine, Oral Pathology* **78**, 494–502.
35. Sundqvist G (1976) Bacteriological studies of necrotic dental pulps. Umeå, Sweden: Umeå University Odontological Dissertations.
36. Sundqvist G (1994) Taxonomy, ecology, and pathogenicity of the root canal flora. *Oral Surgery, Oral Medicine, Oral Pathology* **78**, 522–30.
37. Teixeira FB, Gomes BP, Ferraz CC, Souza-Filho FJ, Zaia AA (2000) Radiographic analysis of the development of periapical lesions in normal rats, sialoadenectomized rats and sialoadenectomized-immunosuppressed rats. *Endodontics and Dental Traumatology* **16**, 154–7.
38. Torabinejad M, Goodacre CJ (2006) Endodontic or dental implant therapy: The factors affecting treatment planning. *Journal of the American Dental Association* **137**, 973–7.
39. Tronstad L (2003) *Clinical endodontics*, 2nd edn. Stuttgart: Thieme.
40. Trope M, Chow E, Nissan R (1995) In vitro endotoxin penetration of coronally unsealed endodontically treated teeth. *Endodontics and Dental Traumatology* **11**, 90–4.
41. Walsh LJ (1997) Serious complications of endodontic infections: Some cautionary tales. *Australian Dental Journal* **42**, 156–9.
42. Weiger R, Manncke B, Werner H, Löst C (1995) Microbial flora of sinus tracts and root canals of non-vital teeth. *Endodontics and Dental Traumatology* **11**, 15–19.
43. Wolcott J, Meyers J (2006) Endodontic re-treatment or implants: a contemporary conundrum. *The Compendium of Continuing Education in Dentistry* **27**, 104–10.
44. Zyrianov GV, Apollonova LA, Bogomazov MIa, Frolova TM (1991) The characteristics of the development of experimental apical periodontitis in irradiation-induced immunodeficiency. [In Russian.] *Stomatologiia (Mosk)* Nov–Dec;(6), 13–15.