REVIEW

Consequences of and strategies to deal with residual post-treatment root canal infection

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Abstract

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Bacterial sampling of prepared root canals is used to determine the presence and character of the remaining microbiota. However, it is likely that current sampling techniques only identify organisms in the main branches of the root canal system whereas it is unlikely that they can sample areas beyond the apical end-point of preparation and filling, or in lateral canals, canal extensions, apical ramifications, isthmuses and within dentinal tubules. Thus, it may be impossible by current techniques to identify residual post-treatment root canal infection. In histologic observations of root apices, bacteria have been found in inaccessible inter-canal isthmuses and accessory canals often in the form of biofilms. There is no *in vivo* evidence to support the assumption that these bacteria can be entombed effectively in the canal system by the root filling and thus be rendered harmless. As a consequence of this residual root infection, post-treatment apical periodontitis, which may be radiographically undetectable, may persist or develop as a defence mechanism to prevent the systemic spread of bacteria and/or their byproducts to other sites of the body. Histologic observation of root apices with surrounding bone removed from either patients or human cadavers has demonstrated that post-treatment apical periodontitis is associated with 50–90% of root filled human teeth. Thus, if the objective of root canal treatment is to eliminate apical periodontitis at a histological level, current treatment procedures are inadequate. It is essential that our knowledge of the local and systemic consequences of both residual post-treatment root infection and post-treatment apical periodontitis be improved. The continued development of treatments that can effectively eliminate root infection is therefore a priority in clinical endodontic research. Post-treatment disease following root canal treatment is most often associated with poor quality procedures that do not remove intra-canal infection; this scenario can be corrected via a nonsurgical approach. However, infection remaining in the inaccessible apical areas, extraradicular infection including apically extruded dentine debris with bacteria present in dentinal tubules, true radicular cysts, and foreign body reactions require a surgical intervention.

Keywords: apical health, apical periodontitis, endodontics, post-treatment disease, root canal infection.

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Introduction

The simplest form of treatment to eliminate apical periodontitis is tooth extraction (Cheung 1996) and there is ample evidence to demonstrate that 1 month after extraction no signs of inflammation remain within

the surrounding tissues (Holland 1992, Mason & Holland 1993), probably because the source of infection has been eliminated. Whilst complete healing is a possibility after root canal treatment delayed apical healing or the persistence of inflammation is sometimes observed (Seltzer 1988, Friedman 2002, Huumonen & Ørstavik 2002). A probable explanation is that treatment may reduce, but not necessarily eliminate root infection (Spångberg & Haapasalo 2002, Trope & Bergenholtz 2002, Haapasalo *et al.* 2003, Bergenholtz & Spångberg 2004). As a consequence, it has been recommended that root-filled teeth without symptoms should be examined radiographically during a follow-up period of up to 4 years to determine whether healing has occurred or whether a diagnosis of post-treatment disease can be made (Strindberg 1956, Seltzer 1988). As a result, post-treatment root infection and post-treatment apical periodontitis may be present for a considerable period of time before a decision is made on whether to revise the root canal treatment, undertake apical surgery or monitor the tooth and periradicular region for a further period of time.

The difference in the healing profile after tooth extraction and after root canal treatment is due to the different conditions under which healing occurs. It is likely that the slower healing taking place after root canal treatment is due in part to the fact that the infection has not been eradicated or reduced sufficiently by the intra-canal treatment procedures (Leonardo *et al.* 1994, Ricucci & Langeland 1998, Nair *et al.* 2005), whereas in the absence of infection following extraction, healing progresses rapidly (Holland 1992, Mason & Holland 1993). It has been demonstrated that after effective endodontic surgery, 97% of cases show radiographic signs of complete healing within 1 year; the average time for lesions to heal was 7 months (Rubinstein & Kim 1999). Large lesions of >10 mm diameter healed within 11 months, indicating that the time required to allow the healing process and bone regeneration in humans can be much shorter than 4 years. At the same time, over-instrumentation, and/or over-filling with resultant extrusion of debris and material during root canal treatment may lead to a slow healing response (Yusuf 1982, Leonardo *et al.* 1997, Ricucci & Langeland 1998, Halse & Molven 2004).

It has now become clear that canal infection is dominated by biofilms consisting of a complex network of different microorganisms imbedded in a matrix (Nair *et al.* 2005) and that bacteria organized in such a way are more resistant than planktonic bacteria to host

defence mechanisms and disinfectants (Costerton *et al.* 1999). Because biofilms are the preferred method of growth on a surface for most species of bacteria, it is likely that bacteria are present in biofilms on the dentinal wall or at the external surface of the root tip (Nair 1987, Siqueira & Lopes 2001, Leonardo *et al.* 2002, Tronstad & Sunde 2003, Nair *et al.* 2005). Bacterial biofilms are reported to be the most common cause of persistent inflammation (Costerton *et al.* 1999) and apical periodontitis has been referred to as 'an intra-radicular biofilm-induced chronic disease' (Nair *et al.* 2005). The effectiveness of conventional treatment procedures to eliminate biofilms within root canal systems remains to be studied (Svensäter & Bergenholtz 2004).

Root canal treatment procedures including access, canal instrumentation, irrigation, intra-canal medication and root filling are performed in an attempt to eradicate infection from the root canal system and eliminate space in order to prevent re-infection. However, the morphology of root canal systems is complex and many human roots have inaccessible areas such as apical canal ramifications, isthmuses and other morphological irregularities (Hess 1925, Pineda & Kuttler 1972), where bacteria may be present in the form of biofilms (Nair *et al.* 2005). For example, communicating isthmuses may be present between mesial canals in many mandibular molars (Ardila *et al.* 2003, Nair *et al.* 2005). In addition, long oval-shaped canals that are difficult to clean are present in approximately one quarter of roots (Wu *et al.* 2000a). Clearly, it is important to appreciate under which conditions conventional treatment procedures are ineffective at eliminating infection.

Recent epidemiological studies in several countries (De Moor *et al.* 2000, Kirkevang *et al.* 2001, Dugas *et al.* 2003), have reported that post-treatment apical periodontitis was radiographically verified in 40–50% of root-filled teeth. Thus, endodontic post-treatment disease is a common finding (Eriksen 1991, Haapasalo *et al.* 2003). The purpose of this report is to review and discuss the occurrence and consequences of and strategies to deal with endodontic post-treatment root infection.

Presence of bacteria in canals after root canal preparation

A vital pulp stump may be present in the apical portion of root canals even in infected cases (Ricucci & Langeland 1998, Spångberg & Haapasalo 2002).

Ricucci & Langeland (1998) reported that the greatest incidence of clinical and radiographic healing occurred when a root filling ended 1.5 or 2 mm short of the radiographic apex. However, in some cases the apical portion of a filled root canal will contain bacteria (Nair *et al.* 1990a, 1999, Simon 1994) that may be associated with inflamed apical periodontal tissues (Nair 2004). Clearly, it is important to determine whether the apical portion of canals contain bacteria (Nair *et al.* 1990a, Simon 1994) or pulp tissue (Ricucci & Langeland 1998, Spångberg & Haapasalo 2002) although this is virtually impossible, particularly under normal clinical conditions.

Baumgartner & Falkler (1991) cultured the apical region of canals in carious exposed teeth with periapical lesions. They found that all canals were infected in the apical 5 mm, with 50 strains of bacteria identified, 34 of which were strict anaerobes. Traditionally, it has been accepted that canals should be prepared to the apical constriction, which lies 0.5–1.0 mm coronally from the foramen (Kuttler 1955, Dummer *et al.* 1984). In this way a small portion of the main canal will remain uninstrumented, along with the many apical ramifications that are often present. Clearly, if all these canal branches are considered the total volume of unprepared canal in any root may be substantial and will contain large numbers of microorganisms.

During canal preparation bacteria, pulp tissue debris and infected dentine particles may be moved apically, often resulting in loss of working length if recapitulation is not performed frequently or is ineffective (West & Roane 1998, Wu *et al.* 2000b). This infected material may be pushed into the apical region beyond the original extent of preparation and even extruded through the foramen (Simon 1994, Wu *et al.* 2000b) with a potentially negative influence on outcome (Simon 1994, Stabholz *et al.* 1994). The bacteria and infected debris accumulating in this most apical portion of the root canal may affect apical healing (Nair *et al.* 1990a, 1999, Simon 1994, West & Roane 1998). One suggested approach to solve the problem is to create a continuously tapering root canal, the apical foramen, rather than the apical constriction, serving as the apical end-point of preparation (West & Roane 1998, Buchanan 2000). Another frequently used technique that is claimed can 'clean' the apical region is the 'apical patency concept' (Cailleteau & Mullaney 1997). This concept involves the periodic use of a small file (size 10 or 15) placed approximately 1 mm longer than the working length in an attempt to push any debris

that has accumulated through the foramen and allow the irrigant solution to bathe the entire apical portion of the canal.

The microbial load is unknown in each individual case. In some cases a vital pulp stump is found apically (Ricucci & Langeland 1998), in others there are bacteria in apical ramifications (Nair 2004). Preparing root canals to the apical foramina in infected canals (Simon 1994, West & Roane 1998, Buchanan 2000) or using a patency file (Cailleteau & Mullaney 1997) may clean the most apical portion of the main canal, but bacteria are likely to remain in lateral and accessory canals or apical ramifications that remain uninstrumented or out of the influence of irrigants. Thus, preparing to the canal terminus does not necessarily result in elimination of root infection. At the same time, patency filing could increase the risk of extruding infected dentine particles, pulp tissue, bacteria and filling materials into the periapical tissues all of which have been associated with persistence of apical periodontitis (Yusuf 1982, Byström *et al.* 1987, Holland 1992, Leonardo *et al.* 1997, Ricucci & Langeland 1998, Molven *et al.* 2002). In addition, it seems likely that the risk of irrigant accidents would increase with patency filing as a clear channel to the periodontal tissues would exist (Ehrich *et al.* 1993, Hülsmann & Hahn 2000). So far, there is no scientific evidence to support the concept that preparing root canals to the apical foramina or the use of patency filing will contribute to healing. A more predicatable and effective procedure to eliminate apical root infection and one that would not result in debris extrusion is orthograde treatment with simultaneous apical surgery (Cheung 1996, Hepworth & Friedman 1997).

It has been reported that the flushing action of conventional hand-delivered irrigation is substantially less effective than that of ultrasonic irrigation to remove debris and bacteria from uninstrumented canal extensions, isthmuses and irregularities (Cunningham *et al.* 1982, Goodman *et al.* 1985, Siqueira *et al.* 1997, Wu & Wesselink 2001, Walters *et al.* 2002, Lee *et al.* 2004). In a study by Cunningham *et al.* (1982), ultrasonics removed 86% of the bacterial spores from the root canal whilst irrigation using a hand syringe removed 62%. In a study by Lee *et al.* (2004), although the apical canal was enlarged to size 50 at the working length and further prepared by stepback instrumentation using sizes 55–80, hand syringe irrigation failed to effectively remove debris from the canal. On the contrary, it has been reported that the quantity of bacteria was reduced substantially in canals that had

been prepared to large sizes and irrigated using hand syringes (Card *et al.* 2002). However, bacteria may be present in areas untouched by paper points used to sample canals with the result that confirming the absence of bacteria with current sampling techniques is unreliable (Molander *et al.* 1998, Nair *et al.* 2005). Clearly, any irrigation regimen may leave bacteria and debris in the canal, but it is clear that ultrasonics is more effective at debridement. However, in routine clinical practice at present it is unlikely that many dentists routinely use ultrasonics during root canal preparation with the result that there is an increased risk of leaving bacteria and debris within the canal system.

Because uninstrumented canal extensions and irregularities may be occupied by debris (Cunningham *et al.* 1982, Goodman *et al.* 1985, Wu & Wesselink 2001, Walters *et al.* 2002, Lee *et al.* 2004), calcium hydroxide and other disinfectants that function only when in direct contact with pathogens (Siqueira & Lopes 1999) will not enter these regions, and will be ineffective (Haapasalo & Ørstavik 1987, Peters *et al.* 2002).

Molander *et al.* (1998) examined the microbiological status of 120 root-filled teeth with or without apical periodontitis when verified radiographically. Using a sampling technique they discovered bacteria in 73% of filled canals associated with radiographic apical periodontitis and in 45% of filled canals without radiographic apical periodontitis. Because 'sampling' in the apical ramification, isthmuses and other canal irregularities was impossible, negative cultures could not assure absence of bacteria. Furthermore, as it was impossible to collect samples from much of the root canal system, the accurate analysis of the quantity and type of bacteria remaining in each root canal was unlikely to reveal the true character of the infection. The authors concluded, 'All root-filled teeth should be regarded as potentially infected' (Molander *et al.* 1998). In a recent study by Nair *et al.* (2005), the apical 3 mm of 16 teeth that were root filled in a single visit was surgically removed on completion of the root canal treatment and examined histologically, bacteria, mostly in the form of biofilms, were found in inaccessible inter-canal isthmi and accessory canals in 14 of the 16 teeth. Some microorganisms showed several dividing forms, indicating presence of vital microorganisms. Microbial sampling would have been impossible in these inaccessible areas. Thus, it can be argued that many filled roots act as implants with low-grade infection embedded within connective tissue (Leonardo *et al.* 1994, Molander *et al.* 1998).

Logically it would appear from the above review that a post-treatment residual infection of the root canal is likely to be present following the use of contemporary treatment procedures. Furthermore, it would seem impossible to eliminate predictably bacteria from the most apical portion of the root canal and the apical ramifications, certainly not without extruding infected debris and/or materials into the apical tissues.

Presence of bacteria in root dentine after canal preparation

Within infected root canals, the inner layer of dentine next to the pulp space contains a large number of microorganisms (Valderhaug 1974, Peters *et al.* 2001). One aim of root canal instrumentation is to remove the inner layer of dentine together with the bacteria (Walton & Torabinejad 1996). However, in many cases bacteria have penetrated deeply into the dentinal tubules to such an extent that they cannot be removed mechanically (Armitage *et al.* 1983, Ando & Hoshino 1990, Peters *et al.* 2001).

Many rotary hand and rotary instrumentation techniques tend to produce round preparations (Vessey 1969, Hülsmann *et al.* 2001), leaving areas of the canal wall uninstrumented, especially in oval canals (Walton 1976, Gambill *et al.* 1996, Evans *et al.* 2001, Wu & Wesselink 2001, Ardila *et al.* 2003, Bergmans *et al.* 2003). Inevitably, as the canal is not instrumented in these regions the infected inner layer of dentine will remain. Recently it has been reported that in oval canals, even circumferential hand filing could only remove the inner layer of dentine from 58% of the circumference of the canal wall, leaving 42% unprepared (Wu *et al.* 2003). Thus, although pressure was applied to the shank of the file towards canal walls in all directions during outward stroking of the instruments, the cutting of the file in the apical root canal was not predictable. Rotary instruments without radial lands can be used in a circumferential motion, but even so, it has been shown that much of the canal wall remains unprepared following their use (Bergmans *et al.* 2003, Peters *et al.* 2003).

Clearly, no technique presently available is able to remove the entire inner layer of infected dentine from a root canal. Consequently, bacteria are likely to remain in dentinal tubules after instrumentation (Leonardo *et al.* 1994, Ricucci & Langeland 1998). It has been reported that the surface tension of sodium hypochlorite limits its ability to spread within the canal (Cunningham & Balekjian 1982). This irrigant solution

is thus unable to penetrate and cleanse narrow, confined portions of root canal systems, particularly dentinal tubules (Senia *et al.* 1971, Salzgeber & Brilliant 1977).

The antimicrobial effect of calcium hydroxide, the most popular intra-canal medicament, is related to the release of hydroxyl ions in an aqueous environment; however, the free radical rarely diffuses away from the bulk of the material (Siqueira & Lopes 1999). In addition, dentine has an inherent buffering capacity to reduce the pH of calcium hydroxide pastes (Wang & Hume 1988). Thus, calcium hydroxide will have a limited lethal effect on bacteria within dentinal tubules and other inaccessible areas such as apical canal ramifications and isthmuses and it remains to be seen if other medicaments, for example, calcium hydroxide combined with chlorhexidine, are more potent (Shuping *et al.* 2000, Sirén *et al.* 2004).

From the above review, it must be concluded that bacteria are likely to remain in dentinal tubules following intra-canal shaping, irrigation and medication procedures.

Entombment of bacteria by the root filling

As instrumentation, irrigation and intra-canal medication procedures cannot remove bacteria predictably from the canal or dentine (Leonardo *et al.* 1994, Molander *et al.* 1998, Bergenholtz & Spångberg 2004), the root filling must serve at least two objectives, that is, to prevent coronal re-infection (Torabinejad *et al.* 1990) and entomb remaining bacteria (Peters *et al.* 1995).

It seems possible to achieve the first objective. For example, Möller *et al.* (1981) sealed access cavities that had been cleaned with 35% hydrogen peroxide, 5% iodine tincture and 70% alcohol with two layers of zinc oxide-sulphate cements and at the end of 6–7 months, all canals remained nonculturable, indicating that coronal leakage had been prevented. Cox *et al.* (1987) placed a layer of ZOE cement over several common coronal restorative materials and found that this 'surface-sealing' layer prevented bacterial penetration.

Entombing bacteria effectively within the root canal system should result in all remaining bacteria being sealed by the root filling in dentinal tubules, in the apical portion of canals, in lateral canals and apical ramification and in the recesses of oval canals and isthmuses so they cannot move into the periodontium. In addition, toxic bacterial elements from multiplying organisms should not be allowed to penetrate into the periodontium in a sufficient quantity to cause inflammation. Therefore, the apical root filling should not contain voids that could allow diffusion of such elements. With present root filling techniques and materials, such strict objectives have not been achieved. In the great majority of dye penetration studies, dye penetrated at least 1 mm from the apical foramen (Wu & Wesselink 1993), indicating that voids invariably existed between the apical root filling and the dentinal wall. Indeed, studies by Torabinejad *et al.* (1990), Chailertvanitkul *et al.* (1997) and by Clark-Holke *et al.* (2003), have demonstrated that these voids allow bacteria to move along the root filling. In addition, it may be difficult to compact materials sufficiently into the apical portion of the root canal without apically extruding debris and material that may itself cause inflammation (Yusuf 1982, Holland 1992, Ricucci & Langeland 1998, Molven *et al.* 2002).

In an *in vitro* study using a sampling technique (Saleh *et al.* 2004), the quantity of *Enterococcus faeccalis* in dentinal tubules was reduced by placement of root fillings containing gutta-percha and some sealers. However, it should not be forgotten that it is impossible to diagnose absence of bacteria in dentinal tubules using conventional sampling techniques *in vivo* (Molander *et al.* 1998).

From the above it may be concluded that there is insufficient evidence to support the assumption that residual bacteria are entombed in the canal system *in vivo* by placement of a root filling.

Limitations of conventional radiographic techniques to diagnose post-treatment apical periodontitis

It is accepted that the absence of a radiolucency does not guarantee the absence of a bony lesion (Bender & Seltzer 1961, Bender 1982, van der Stelt 1985, Huumonen & Ørstavik 2002), yet the absence of an apical radiolucency is considered to represent health.

Post-treatment apical periodontitis with bone loss may not result in an apical radiolucency, depending on the density and thickness of the overlying cortical bone, and the distance between the lesion and the cortical bone (Bender & Seltzer 1961, Bender 1982, van der Stelt 1985, Huumonen & Ørstavik 2002). When a bone lesion is within the cancellous bone and the overlying cortical bone is substantial, the bone lesion is not visible radiographically. Therefore, post-treatment apical periodontitis can be radiographically visible or invisible. Clinically, it has been reported that a large

lesion of up to 8 mm in diameter can be present without a radiolucency (Stabholz *et al.* 1994, Ricucci & Bergenholtz 2003). In animal experiments with dogs, post-treatment apical periodontitis was often present within the cancellous bone without involving the cortical bone (Katebzadeh *et al.* 1999).

In two studies where the relationship between histologic and radiologic signs of inflammation was determined in human cadavers, the negative predictive value of radiologic inflammatory signs was 53% and 67%, respectively (Brynolf 1967, Barthel *et al.* 2004). In an animal study, the positive predictive value of radiologic signs in dogs was 100% and the negative predictive value of radiologic signs was 55% (Rowe & Binnie 1974). This means that whenever an apical lucency was detected radiographically, it always corresponded histologically with mild or severe inflammation; however, when an intact periradicular region was diagnosed radiographically, only 55% of the cases were uninflamed histologically.

From the above, it must be concluded that conventional radiographic techniques lack sufficient sensitivity to serve as a reliable means for diagnosing post-treatment health. Therefore, the absence of a radiolucency does not prove that residual bacteria have been entombed in the canal system by placement of a root filling and thus rendered harmless.

Presence of post-treatment apical periodontitis diagnosed by histology and the periapical index

In three studies where root-filled teeth in cadavers were examined histologically 93%, 51% and 52% of filled teeth had post-treatment apical periodontitis, respectively (Brynolf 1967, Green *et al.* 1997, Barthel *et al.* 2004). However, the quality of the root fillings in some cases was not good or not assessed and it is unknown whether this was a confounding variable. At the same time, the tissues had been fixed in formalin and stored for unknown periods (Barthel *et al.* 2004) with the result that many inflammatory cells might have become invisible due to improper fixation.

In an *in vivo* histological study by Ricucci & Langeland (1998), the root apex and periapical tissues were examined histologically following root canal treatment. A strict aseptic technique was applied. Each canal was irrigated with copious amounts of 1% NaOCl using a syringe and then filled with laterally condensed gutta-percha points and sealer. Of the 49 treated roots, 22 including 13 with a vital pulp and nine with a

necrotic pulp were followed up for at least 3 years following treatment. The average observation period was 5 years and 4 months (ranging from 3 years to 10 years 8 months). In 18 (82%) of the 22 roots the canal was filled 0–2 mm from the radiographic apex. However, the authors stated that 'Despite careful preparation of optimal access and meticulous root canal cleaning and shaping, in all cases remnants of pulp tissue and dentine chips were found at different levels of the root canals' (Ricucci & Langeland 1998). At the end of the observation period, despite the fact that 18 (82%) of the 22 roots did not have an apical radiolucency, only three (14%) of them were free of inflammatory cells within the surrounding bone or fragments of periodontal ligament attached to the extracted roots (Ricucci & Langeland 1998). When the root was filled short, inflammatory cells were seen in the residual pulp tissue; when the canal was filled flush with the apex or over-filled, severe inflammation was seen in the periapical tissue. As the development of apical periodontitis creates a barrier within the body to prevent further spread of microorganisms (Stashenko 1990, Siqueira 2001, Bergenholtz & Spångberg 2004) it could be that when the most apical portion was not infected, periapical involvement was mild. When the most apical portion of the root had become infected, severe apical periodontitis occurred. On the contrary, irritation from root filling materials could have been another factor that sustained the inflammatory response (Brynolf 1967, Bergenholtz *et al.* 1979, Yusuf 1982, Holland 1992, Ricucci & Langeland 1998, Molven *et al.* 2002). Thus, post-treatment apical periodontitis can vary in terms of its extent and severity; whether a mild asymptomatic apical periodontitis should be treated is discussed later.

Some investigators have used the periapical index (PAI) to assess the outcome of root canal treatment (Ørstavik *et al.* 1987, 2004, Waltimo *et al.* 2001). The PAI is based on reference radiographs with verified histological diagnoses originally published by Brynolf (1967). The PAI has been found to be a useful tool that reflects histological diagnosis and ensures unbiased assessment of the periapical condition (Ørstavik *et al.* 1987, 2004, Waltimo *et al.* 2001). The PAI radiographic scores 1 (normal apical periodontium on the radiograph) to 5 (worst apical radiolucency) correspond to different points in a ridit scale that reflected histologic inflammatory status from no inflammation (ridit 0.036) to severe inflammation (ridit 0.964). In a clinical 4-year follow-up study (Ørstavik *et al.* 1987), the average ridits of

those cases with high pre-treatment PAI ridit decreased from >0.6 to 0.25 during the first 2 years after treatment, however, little change occurred over the following 2 years. In another clinical 4-year follow-up study (Waltimo *et al.* 2001), root canals were filled with gutta-percha and three different sealers; at the end of 4 years, the average ridit was 0.24, 0.22 and 0.31, respectively, which represents apical periodontitis of low severity (Ørstavik *et al.* 1987). The rationale to include PAI score 2 (ridit 0.24) in the success-category (Ørstavik *et al.* 1987, 2004) was based most probably on a concern for overdiagnosing disease. However, considering that cases with score 2 occupied 30% of all cases at the end of the study (Ørstavik *et al.* 1987), it can be assumed that many cases with a small lesion were included in the success-category.

In experiments with dogs and monkeys (Seltzer *et al.* 1964, Snyder *et al.* 1966, Malooley *et al.* 1979), teeth were root filled and histologically examined after 5–12 months. The authors reported that 'Repair of the periapical tissues did not occur uniformly in all teeth that were treated'. In a study by Tanomaru Filho *et al.* (1998) the teeth of dogs with induced chronic apical periodontitis were instrumented, irrigated with 5.25% NaOCl and dressed with calcium hydroxide for 1 week before filling with lateral condensation of gutta-percha and either calcium hydroxide or ZnOE-based sealer. Histologically, periapical inflammation persisted in most cases at 270 days. In the dog, the anatomy of the apical portion of the root canal differs from that in humans as it consists of a delta of many small canals that cannot be cleaned nor filled (Holland 1992). The poor healing suggests that infection remaining in the apical delta caused post-treatment apical periodontitis. Furthermore, in an animal experiment with ferrets (Holland 1992), post-treatment apical periodontitis was present in many cases 12 months after performing vital pulpectomy in normal teeth. In the uninfected control group of a study by Katebzadeh *et al.* (1999), vital pulpectomy was performed on the teeth of healthy dogs, periapical inflammation of different degrees was verified in 'a surprisingly high number of cases'. In a study reported by Leonardo *et al.* (1997), vital pulpectomy was performed on the teeth of 68 healthy dogs, similarly poor findings were seen when CRCS (Hygenic), Apexit (Vivadent) or Sealer 26 (Dentsply Ind. Com. Ltda., Petrópolis, RJ, Brazil) was used as sealer. However, when Sealapex (Sybron/Kerr Indústria e Comércio Ltda., Guarulhos,

SP, Brazil) was the sealer, periapical inflammation was absent at 6 months. The histological findings of vital pulpectomy in dog and ferret teeth (Holland 1992, Leonardo *et al.* 1997, Katebzadeh *et al.* 1999) suggest that in certain situations root canal treatment may lead to periapical inflammation.

From the above it is concluded that histologically, post-treatment apical periodontitis is likely to be present in more than half of root filled human teeth.

Potential systemic effects of post-treatment residual infection and post-treatment apical periodontitis

Whether a long-standing canal infection and apical periodontitis will influence general health has been discussed for over a century (Grossman 1974), but no definite conclusion has emerged (Rogers 1976, Ehrmann 1977, Thoden van Velzen *et al.* 1984, Mattila *et al.* 1989, 1995, Marton & Kiss 1992, Ridker *et al.* 1997, 2000, 2001, Debelian *et al.* 1998, Slavkin 1999, Loos *et al.* 2000, Murray & Saunders 2000, Li *et al.* 2001, Haueisen & Heidemann 2002, Frisk *et al.* 2003, Janket *et al.* 2003, Meurman *et al.* 2003, Skaug 2003, Caplan *et al.* 2004).

Recently, long-standing inflammation has been related to the risk of cardiovascular diseases. In a study where plasma C-reactive protein (CRP), a marker for systemic inflammation, was measured in 1068 male adults, half developed coronary heart disease (CHD) over the course of a 14-year study (Ridker *et al.* 1997). It was found that those with very low levels of CRP, <0.5 mg L^{-1}, rarely had CHD; however, when CRP was higher than 1.0 mg L^{-1}, the risk of CHD was increased (Ridker *et al.* 1997, Loos *et al.* 2000). Risks were stable over long periods, were not modified by smoking, and were independent of other lipid-related and nonlipid-related risk factors (Ridker *et al.* 1997). In the study by Loos *et al.* (2000), localized and generalized periodontitis were associated with significantly higher systemic levels of CRP; importantly, the possible confounding factors including smoking, hypertension, cholesterol, etc. had been controlled. Thus, it is of concern whether long-standing apical periodontitis of endodontic origin also elevates systemic levels of CRP in human (Marton & Kiss 1992). Buttke *et al.* (2005) have recently reported that chronic apical periodontitis is not associated with elevated CRP in dogs.

According to the original concept, focal infection occurs when microorganisms disseminate from a localized area of infection (infected canal) through the

blood circulation and establish themselves elsewhere in the body as a secondary infection (Skaug 2003). Passage of microorganisms into the blood stream following endodontic procedures has been examined and it has been reported that endodontic treatment procedures may cause a bacteraemia (Debelian *et al.* 1998, Savarrio *et al.* 2005). Researchers tended to isolate the same bacteria from the original and secondary diseased organs (Skaug 2003).

Currently, links between dental infections and CHD or adverse pregnancy outcomes are being investigated (Caplan 2004). It is now hypothesized that long-standing, low-grade infection may activate immune cells: certain parts of the body are mistakenly selected by immune cells for attack; e.g. macrophages begin attacking cholesterol deposits in the coronary arteries, causing the plaque to burst, and provoke CHD (Ridker *et al.* 1997, 2000, 2001). These assumptions remain to be evaluated further. The Total Dental Index is used as a summary measure of total dental infections. It has been so far agreed in a few studies (DeStefano *et al.* 1993, Mattila *et al.* 1993, 1995, 2000, Mattila 1993, Joshipura *et al.* 1996, Frisk *et al.* 2003, Hung *et al.* 2004) that the Total Dental Index and tooth loss are significantly associated with CHD. Both periodontitis and apical periodontitis are contributors to either the Total Dental Index or the tooth loss.

In an epidemiologic study reported recently (Caplan *et al.* 2004), during a maximum follow-up of 32 years with 708 male adults, lesions of endodontic origin amongst those <40 years old were statistically significantly associated with risk of CHD after controlling for baseline values of education, income, total cholesterol, triglycerides, diabetes, hypertension and smoking. Frisk *et al.* (2003) investigated links between endodontic variables and CHD. Positive significant associations were found between tooth loss and CHD, also between subjects with two root-filled teeth and CHD, but for periapical radiolucency the logistic regression analysis did not support an association with CHD. However, these studies (Frisk *et al.* 2003, Caplan *et al.* 2004) have a drawback that the category of individuals without apical periodontitis contained many individuals with radiographically undetectable apical periodontitis due to the insensitivity of the negative radiographic diagnosis (Bender & Seltzer 1961, Bender 1982, van der Stelt 1985, Huumonen & Ørstavik 2002). Actually, the capacity of such studies to discover the association between apical periodontitis and CHD is limited. Therefore, failing to discover the link does not prove the absence of the link.

From the above, it is concluded that long-standing inflammation may have systemic effects and influence general health. Thus, it is necessary to develop procedures that reduce root infection to a level that eliminates periapical inflammation.

Strategies to deal with post-treatment disease

Ørstavik & Pitt Ford (1998), Friedman (2002) and Trope (2003) have defined clinical endodontics as the prevention and/or elimination of apical periodontitis. Accordingly, the aim of endodontic treatment is to achieve histological healing, i.e. absence of post-treatment apical periodontitis not only at a radiographic level but also at a histological level.

Epidemiological studies have shown that post-treatment disease is quite common. In a Lithuanian population, the frequency of radiographically verified post-treatment apical periodontitis was 35% (Sidaravicius *et al.* 1999). Similarly verified post-treatment apical periodontitis was observed in 40% of root-filled teeth in a Belgian population (De Moor *et al.* 2000). In a study in Denmark (Kirkevang *et al.* 2001), the periapical status of nearly 600 root-filled teeth was compared in 1974–1975 and 1997–1998. Post-treatment apical periodontitis was observed in approximately 50% of the root-filled teeth in both groups, and in molars the prevalence of post-treatment apical periodontitis was as high as 65% in both groups. In two selected Canadian populations the prevalence of post-treatment apical periodontitis was 44% and 51% (Dugas *et al.* 2003). Considering that many lesions limited to cancellous bone are not detected with conventional radiographic techniques, the prevalence of periapical radiolucencies in these studies must be an underestimation of the real prevalence of disease. The high prevalence of apical lesions is likely to be due to improper root canal treatment failing to reduce markedly the bacterial load or coronal leakage.

Common problems that cause persistent post-treatment periapical pathosis have been widely documented (Wu & Wesselink 2006). These problems include infection remaining in the apical inaccessible areas (Nair 2004, Nair *et al.* 2005), extraradicular infection (Sundqvist & Reuterving 1980, Tronstad *et al.* 1987, Siqueira & Lopes 2001, Leonardo *et al.* 2002, Tronstad & Sunde 2003) including apically extruded dentine debris with bacteria present in dentinal tubules (Yusuf 1982), radicular true cyst (Nair *et al.* 1993, Simon 1998), foreign body reaction (Nair *et al.* 1990b, 1998,

Nair 1998, Ricucci & Langeland 1998), poor root canal therapies with or without iatrogenically altered root canal morphology (Ray & Trope 1995, Tronstad *et al.* 2000, Gorni & Gagliani 2004), and vertical root fractures (Vire 1991, Testori *et al.* 1993, Tamse *et al.* 1999). Poor root canal therapies may be corrected nonsurgically; the other problems may require a surgical intervention.

Apical surgery offers immediate access to the root apex. The periapical pathological tissues are removed by apical curettage and the apical portion of the root, which frequently contains infected canal ramifications (Rubinstein & Kim 1999, Nair *et al.* 2005) is removed by resection. Importantly, at surgery the prepared apical canals and exposed isthmuses and accessory canals (Weller *et al.* 1995, Von Arx 2005) should be carefully located and prepared with the aid of a surgical operation microscope and micromirror (Rubinstein & Kim 1999) and then, irrigated ultrasonically to remove bacteria, debris and smear layer (Lee *et al.* 2004) prior to their filling. Ninety-seven per cent of the lesions including those >10 mm in diameter completely healed within 1 year after effective apical surgery (Rubinstein & Kim 1999). Ideally, apical surgery and orthograde retreatment should be performed simultaneously (Hepworth & Friedman 1997) because endodontic surgery is not a long-term solution for inadequate orthograde root canal treatment (Rubinstein & Kim 1999).

However, dentists and patients may have different attitudes to the presence and treatment of post-treatment root canal infection and post-treatment apical periodontitis in terms of their relevance (Reit & Kvist 1998). If the negative predictive value of radiolucency is 60% and post-treatment apical periodontitis has been demonstrated in the other 40% at a histological level (Brynolf 1967, Rowe & Binnie 1974, Barthel *et al.* 2004), one may argue why is 'absence of apical radiolucency' necessary? It has been reported in an epidemiological study on outcomes of endodontic treatment in a large American patient population that 97% of teeth were retained in the oral cavity 8 years following nonsurgical root canal treatment (Salehrabi & Rotstein 2004). Clearly, many of these teeth must have been associated with post-treatment root canal infection and post-treatment apical periodontitis. Accepting that the persistence of low-grade post-treatment apical periodontitis is a frequent consequence of many root canal treatments, it could be argued that it may be appropriate to not treat teeth with mild asymptomatic apical periodontitis or a minimal radiographic periapical pathosis. However, considering that sometimes a large bony lesion may be present without an obvious radiolucency using conventional radiographic techniques (Stabholz *et al.* 1994, Ricucci & Bergenholtz 2003), how should a 'tolerable low-grade inflammation' or 'minimal radiographic periradicular pathosis' be defined? Clearly, more effort and resource should be directed into better diagnostic methods. Furthermore, if asymptomatic inflammation remaining after endodontic treatment is considered acceptable, treating asymptomatic lesions associated with teeth that have not received endodontic treatment may be questioned.

From this review it appears to be important to prevent pulpal infection because it is difficult to eliminate bacteria and biofilms from the root canal system, especially from the most apical portion of the root canal and apical ramifications (Nair *et al.* 1990a, 2005, Nair 2004). Furthermore, when the apical portion of the root has been infected, bacterial biofilms may occasionally be present on the external surface of the root tip (Siqueira & Lopes 2001, Leonardo *et al.* 2002, Tronstad & Sunde 2003). It is therefore preferable to perform root canal treatment in cases where the apical portion of the root has not been infected using a technique that prevents apical spread of microorganisms. When the apical portion has been infected already, including retreating root-filled teeth with post-treatment disease, patients should be informed that performing nonsurgical conventional root canal treatment or retreatment may provide relief of symptoms and retain a functional tooth, however, some infection and inflammation may remain.

Conclusions

Apical periodontitis, which may be radiographically undetectable, is likely to persist or emerge in most root-filled teeth as a consequence of residual endodontic post-treatment root infection. If the objective of root canal treatment is defined as elimination of apical periodontitis at a histological level, current treatment procedures must be improved. At the same time, it is essential that further knowledge is acquired of the local and systemic biological consequences of residual post-treatment root infection and post-treatment apical periodontitis.

Acknowledgement

References

Ando N, Hoshino E (1990) Predominant obligate anaerobes invading the deep layers of root canal dentine. *International Endodontic Journal* **23**, 20–7.

Ardila CN, Wu M-K, Wesselink PR (2003) Percentage of filled canal area in mandibular molars after conventional root-canal instrumentation and after a noninstrumentation technique (NIT). *International Endodontic Journal* **36**, 591–8.

Armitage GC, Ryder MI, Wilcox SE (1983) Cemental changes in teeth with heavily infected root canals. *Journal of Endodontics* **9**, 127–30.

Barthel CR, Zimmer S, Trope M (2004) Relationship of radiologic and histologic signs of inflammation in human root-filled teeth. *Journal of Endodontics* **30**, 75–9.

Baumgartner JC, Falkler WA Jr (1991) Bacteria in the apical 5 mm of infected root canals. *Journal of Endodontics* **17**, 380–3.

Bender IB (1982) Factors influencing the radiographic appearance of bone lesions. *Journal of Endodontics* **8**, 161–70.

Bender IB, Seltzer S (1961) Roentgenographic and direct observation of experimental lesions in bone: I. *Journal of American Dental Association* **62**, 152–60.

Bergenholtz G, Spångberg L (2004) Controversies in endodontics. *Critical Reviews in Oral Biology and Medicine* **15**, 99–114.

Bergenholtz G, Lekholm U, Milthon R, Engstrom B (1979) Influence of apical overinstrumentation and overfilling on re-treated root canals. *Journal of Endodontics* **5**, 310–4.

Bergmans L, Van Cleynenbreugel J, Beullens M, Wevers M, Van Meerbeek B, Lambrechts P (2003) Progressive versus constant tapered shaft design using NiTi rotary instruments. *International Endodontic Journal* **36**, 288–95.

Brynolf I (1967) A histological and roentgenological study of periapical region of human upper incisors. *Odontologisk Revy* **18**(Suppl. 11), 1–97.

Buchanan LS (2000) The standardized-taper root canal preparation – Part 1. Concepts for variably tapered shaping instruments. *International Endodontic Journal* **33**, 516–29.

Buttke TM, Shipper G, Delano EO, Trope M (2005) C-reactive protein and serum amyloid a in a canine model of chronic apical periodontitis. *Journal of Endodontics* **31**, 728–32.

Byström A, Happonen RP, Sjögren U, Sundqvist G (1987) Healing of periapical lesions of pulpless teeth after endodontic treatment with controlled asepsis. *Endodontics & Dental Traumotology* **3**, 58–63.

Cailleteau JG, Mullaney TP (1997) Prevalence of teaching apical patency and various instrumentation and obturation techniques in United States dental schools. *Journal of Endodontics* **23**, 394–6.

Caplan DJ (2004) Epidemiologic issues in studies of association between apical periodontitis and systemic health. *Endodontic Topics* **8**, 15–35.

Caplan DJ, Chasen JB, Cai J et al. (2004) Lesions of endodontic origin and risk of coronary heart disease. *Journal of Dental Research* **83**, (Special Issue A), Abstract 1323.

Card SJ, Sigurdsson A, Ørstavik D, Trope M (2002) The effectiveness of increased apical enlargement in reducing intracanal bacteria. *Journal of Endodontics* **28**, 779–83.

Chailertvanitkul P, Saunders WP, Saunders EM, Mackenzie D (1997) An evaluation of microbial coronal leakage in the restored pulp chamber of root-canal treated multirooted teeth. *International Endodontic Journal* **30**, 318–22.

Cheung GSP (1996) Endodontic failures – changing the approach. *International Dental Journal* **46**, 131–8.

Clark-Holke D, Drake D, Walton R, Rivera E, Gutmiller JM (2003) Bacterial penetration through canals of endodontically treated teeth in the presence or absence of the smear layer. *Journal of Dentistry* **31**, 275–81.

Costerton JW, Stewart PS, Greenberg EP (1999) Bacterial biofilms: a common cause of persistent infections. *Science* **284**, 1318–22.

Cox CF, Keall CL, Keall HJ, Ostro E, Bergenholtz G (1987) Biocompatibility of surface-sealed dental materials against exposed pulp. *Journal of Prosthetic Dentistry* **57**, 1–8.

Cunningham WT, Balekjian AY (1982) Effect of alcohol on the spreading ability of sodium hypochlorite endodontic irrigant. *Oral Surgery, Oral Medicine, and Oral Pathology* **54**, 333–5.

Cunningham WT, Martin H, Pelleu GB, Stoops DE (1982) A comparison of antimicrobial effectiveness of endodontic and hand root canal therapy. *Oral Surgery, Oral Medicine, and Oral Pathology* **54**, 238–41.

De Moor RJG, Hommez GMG, De Boever JG, Delmé KIM, Martens GEI (2000) Periapical health related to the quality of root canal treatment in a Belgian population. *International Endodontic Journal* **33**, 113–20.

Debelian G, Olsen I, Tronstad L (1998) Anaerobic bacteremia and fungemia in patients undergoing endodontic therapy: an overview. *Annals of Periodontology* **3**, 281–7.

DeStefano F, Anda RF, Kahn HS, Williamson DF (1993) Dental disease and risk for coronary heart disease and mortality. *British Medical Journal* **306**, 688–91.

Dugas NN, Lawrence HP, Teplitsky PE, Pharoah MJ, Friedman S (2003) Periapical health and treatment quality assessment of root-filled teeth in two Canadian populations. *International Endodontic Journal* **36**, 181–92.

Dummer PMH, McGinn JH, Rees DG (1984) The position and topography of the apical canal constriction and apical foramen. *International Endodontic Journal* **17**, 192–8.

Ehrich DG, Brian JD Jr, Walker WA (1993) Sodium hypochlorite accident inadvertent injection into the maxillary sinus. *Journal of Endodontics* **19**, 180–2.

Ehrmann EH (1977) Focal infection. The endodontic point of view. *Oral Surgery, Oral Medicine, and Oral Pathology* **44**, 628–34.

Eriksen HM (1991) Endodontology – epidemiology considerations. *Endodontics & Dental Traumatology* **7**, 189–95.

Evans GE, Speight PM, Gulabivala K (2001) The influence of preparation technique and sodium hypochlorite on removal of pulp and predentine from root canals of posterior teeth. *International Endodontic Journal* **34**, 322–30.

Friedman S (2002) Considerations and concepts of case selection in the management of post-treatment endodontic disease (treatment failure). *Endodontic Topics* **1**, 54–78.

Frisk F, Hakeberg M, Ahlqwist M, Bengtsson C (2003) Endodontic variables and coronary heart disease. *Acta Odontologica Scandinavica* **61**, 258–62.

Gambill JM, Alder M, del Rio CE (1996) Comparison of nickel-titanium and stainless steel hand-file instrumentation using computed tomography. *Journal of Endodontics* **22**, 369–75.

Goodman A, Beck M, Melfi R, Meyers W (1985) An in vitro comparison of the efficacy of the step-back technique versus a step-back/ultrasonic technique in human mandibular molars. *Journal of Endodontics* **11**, 249–56.

Gorni FG, Gagliani MM (2004) The outcome of endodontic retreatment: a 2-yr follow-up. *Journal of Endodontics* **30**, 1–4.

Green TL, Walton RE, Taylor JK, Merrell P (1997) Radiographic and histologic periapical findings of root canal treated teeth in cadaver. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **83**, 707–11.

Grossman LI (1974) Endodontics: a peep into the past and the future. *Oral Surgery, Oral Medicine, and Oral Pathology* **37**, 599–610.

Haapasalo M, Ørstavik D (1987) In vitro infection and disinfection of dentinal tubules. *Journal of Dental Research* **66**, 1375–9.

Haapasalo M, Dunæs T, Endal U (2003) Persistent, recurrent, and acquired infection of the root canal system post-treatment. *Endodontic Topics* **6**, 29–56.

Halse A, Molven O (2004) Increased width of the apical periodontal membrane space in endodontically treated teeth may represent favourable healing. *International Endodontic Journal* **37**, 552–60.

Haueisen H, Heidemann D (2002) Hemisection for treatment of an advanced endodontic-periodontal lesion: a case report. *International Endodontic Journal* **35**, 557–72.

Hepworth MJ, Friedman S (1997) Treatment outcome of surgical and non-surgical management of endodontic failures. *Journal of Canadian Dental Association* **63**, 364–71.

Hess W (1925) *The Anatomy of the Root Canals of the Teeth of the Permanent and Deciduous Dentitions.* New York: William Wood & Co.

Holland GR (1992) Periapical innervation of the ferret canine one year after pulpectomy. *Journal of Dental Research* **71**, 470–4.

Hülsmann M, Hahn W (2000) Complications during root canal irrigation - literature review and case reports. *International Endodontic Journal* **33**, 186–93.

Hülsmann M, Schade M, Schäfers F (2001) A comparative study of root canal preparation with HERO 642 and Quantec SC rotary Ni-Ti instruments. *International Endodontic Journal* **34**, 538–46.

Hung H-C, Joshipura KJ, Colditz G, Manson JE (2004) The association between tooth loss and coronary heart disease in men and women. *Journal of Public Health Dentistry* **64**, 209–15.

Huumonen S, Ørstavik D (2002) Radioological aspects of apical periodontitis. *Endodontic Topics* **1**, 3–25.

Janket S-J, Baird AE, Chuang S-K, Jones JA (2003) Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **95**, 559–69.

Joshipura K, Rimm E, Douglass C (1996) Poor oral health and coronary heart disease. *Journal Dental Research* **75**, 1631–6.

Katebzadeh N, Hupp J, Trope M (1999) Histological periapical repair after obturation of infected root canals in dogs. *Journal of Endodontics* **25**, 364–8.

Kirkevang LL, Horsted-Bindslev P, Ørstavik D, Wenzel A (2001) A comparison of the quality of root canal treatment in two Danish subpopulations examined 1974–75 and 1997–98. *International Endodontic Journal* **34**, 607–12.

Kuttler Y (1955) Microscopic investigation of root apexes. *Journal of American Dental Association* **50**, 544–52.

Lee S-J, Wu M-K, Wesselink PR (2004) The ability of syringe irrigation and ultrasound irrigation to remove dentin debris from uninstrumented extensions and irregularities in root canals. *International Endodontic Journal* **37**, 672–8.

Leonardo MR, Almeida WA, Ito IY, da Silva LAB (1994) Radiographic and microbiologic evaluation of posttreatment apical and periapical repair of root canals of dogs' teeth with experimentally induced chronic lesion. *Oral Surgery, Oral Medicine, and Oral Pathology* **78**, 232–8.

Leonardo MR, Silva LAB, Utrilla LS, Assed S, Ether SS (1997) Calcium hydroxide root canal sealers – histopathologic evaluation of apical and periapical repair after endodontic treatment. *Journal of Endodontics* **23**, 428–32.

Leonardo MR, Rossi MA, Silva LAB, Ito IY, Bonifácio KC (2002) EM evaluation of bacterial biofilms and microorganisms on the apical external root surface of human teeth. *Journal of Endodontics* **28**, 815–8.

Li X, Kolltveit KM, Tronstad L, Olsen I (2001) Systemic diseases caused by oral infection. *Clinical Microbiology Reviews* **13**, 547–58.

Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PME, van der Velden U (2000) Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *Journal of Periodontology* **71**, 1528–34.

Malooley J Jr, Patterson SS, Kafrawy A (1979) Response of periapical pathosis to endodontic treatment in monkeys. *Oral Surgery, Oral Medicine, and Oral Pathology* **47**, 545–54.

Marton IJ, Kiss C (1992) Influence of surgical treatment of periapical lesions on serum and blood levels of inflammatory mediators. *International Endodontic Journal* **25**, 229–33.

Mason AG, Holland GR (1993) The reinnervation of healing extraction sockets in the ferret. *Journal of Dental Research* **72**, 1215–21.

Mattila KJ (1993) Dental infections as a risk factor for acute myocardial infarction. *European Heart Journal* **14**, 51–3.

Mattila KJ, Nieminen MS, Voltonen VV, Rasi VP (1989) Association between dental health and acute myocardial infection. *British Medical Journal* **298**, 779–81.

Mattila KJ, Valle MS, Nieminen MS, Voltonen VV (1993) Dental infections and coronary atherosclerosis. *Atherosclerosis* **103**, 205–11.

Mattila KJ, Voltonen VV, Nieminen MS, Huttunen JK (1995) Dental infection and the risk of new coronary events: prospective study of patients with documented coronary artery disease. *Clinical Infectious Diseases* **20**, 588–92.

Mattila KJ, Asikainen S, Wolf J, Jousimies-Somer H (2000) Age, dental infections and coronal heart disease. *Journal of Dental Research* **79**, 756–60.

Meurman JH, Janket S-J, Qvarnström M, Nuutinen P (2003) Dental infections and serum inflammatory markers in patients with and without severe heart disease. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **96**, 695–700.

Molander A, Reit C, Dahlbaren G, Kvist T (1998) Microbiological status of root-filled teeth with apical periodontitis. *International Endodontic Journal* **31**, 1–7.

Möller AJR, Fabricius L, Dahlbaren G, Öhman AE, Heyden AG (1981) Influence on periapical tissues of indigenous oral bacteria and necrotic pulp tissue in monkeys. *Scandinavian Journal of Dental Research* **89**, 475–84.

Molven O, Halse A, Fristad I (2002) Long-term reliability and observer comparisons in the radiographic diagnosis of periapical disease. *International Endodontic Journal* **35**, 142–7.

Murray CA, Saunders WP (2000) Root canal treatment and general health: a review of the literature. *International Endodontic Journal* **33**, 1–18.

Nair PNR (1987) Light and electron microscopic studies of root canal flora and periapical lesions. *Journal of Endodontics* **13**, 29–39.

Nair PNR (1998) Pathology of apical periodontitis. In: Ørstavik D, Pitt Ford TR, eds. *Essential Endodontology.* Oxford, UK: Blackwell Science Ltd, pp. 68–105.

Nair PNR (2004) Pathogenesis of apical periodontitis and the causes of endodontic failures. *Critical Reviews in Oral Biology and Medicine* **15**, 348–81.

Nair PNR, Sjögren U, Krey G, Kahnberg K-E, Sundquvist G (1990a) 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**, 589–95.

Nair PNR, Sjögren U, Krey G, Sundquvist G (1990b) Therapy-resistant foreign body giant cell granuloma at the periapex of a root-filled human tooth. *Journal of Endodontics* **16**, 589–95.

Nair PNR, Sjögren U, Schmacher E, Sundquvist G (1993) Radicular cyst affecting a root-filled human tooth: a long-term post-treatment follow-up. *International Endodontic Journal* **26**, 225–33.

Nair PNR, Sjögren U, Sundquvist G (1998) Cholesterol crystals as an etiological factor in non-resolving chronic inflammation: an experimental study in guinea pigs. *European Journal of Oral Sciences* **106**, 644–50.

Nair PNR, Sjögren U, Figdor D, Sundquvist G (1999) Persistent periapical radiolucencies of root-filled human teeth, failed endodontic treatments, and periapical scars. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **87**, 617–27.

Nair PNR, Henry S, Cano V, Vera J (2005) Microbial status of apical root canal system of human mandibular first molars with primary apical periodontitis after ''one-visit'' endodontic treatment. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **99**, 231–52.

Ørstavik D, Pitt Ford TR (1998) Apical periodontitis: microbial infection and host responses. In: Ørstavik D, Pitt Ford TR, eds. *Essential Endodontology.* Oxford: Blackwell Science, pp. 1–8.

Ørstavik D, Kerekes K, Eriksen HM (1987) Clinical performance of three endodontic sealers. *Endodontics & Dental Traumatology* **3**, 178–86.

Ørstavik D, Qvist V, Stoltze K (2004) A multivariate analysis of the outcome of endodontic treatment. *European Journal of Oral Sciences* **112**, 224–30.

Peters LB, Wesselink PR, Moorer WR (1995) The fate and the role of bacteria left in root dentinal tubules. *International Endodontic Journal* **28**, 95–9.

Peters LB, Wesselink PR, Buys JF, van Winkelhoff AJ (2001) Viable bacteria in root dentinal tubules of teeth with apical periodontitis. *Journal of Endodontics* **27**, 76–81.

Peters LB, van Winkelhoff A-J, Buijs JF, Wesselink PR (2002) Effects of instrumentation, irrigation and dressing with calcium hydroxide on infection in pulpless teeth with periapical bone lesions. *International Endodontic Journal* **35**, 13–21.

Peters OA, Peters CI, Schönenberger K, Barbakow F (2003) ProTaper rotary root canal preparation: assessment of torque and force in relation to canal anatomy. *International Endodontic Journal* **36**, 93–9.

Pineda F, Kuttler Y (1972) Mesiodistal and buccolingual roentgenographic investigation of 7275 root canals. *Oral Surgery, Oral Medicine, and Oral Pathology* **32**, 101–10.

Ray HA, Trope M (1995) Periapical status of endodontically treated teeth in relation to the technical quality of the root fillings and the coronal restoration. *International Endodontic Journal* **28**, 12–8.

Reit C, Kvist T (1998) Endodontic retreatment behaviour: the influence of diseases concepts and personal values. *International Endodontic Journal* **31**, 358–63.

Ricucci D, Bergenholtz G (2003) Bacterial status in root-filled teeth exposed to the oral environment by loss of restoration

and fracture or caries – a histobacteriological study of treated cases. *International Endodontic Journal* **36**, 787–802.

Ricucci D, Langeland K (1998) Apical limit of root canal instrumentation and obturation, part 2. A histological study. *International Endodontic Journal* **31**, 394–409.

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *The New England Journal of Medicine* **336**, 973–9.

Ridker PM, Hennekens CH, Buring JE, Rifai N (2000) C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *The New England Journal of Medicine* **342**, 836–43.

Ridker PM, Stampfer MJ, Rifai N (2001) Novel risk factors for systemic atherosclerosis. *Journal of American Medical Association* **285**, 2481–5.

Rogers AH (1976) The oral cavity as a source of potential pathogens in focal infection. *Oral Surgery, Oral Medicine, and Oral Pathology* **42**, 245–8.

Rowe AHR, Binnie WH (1974) Correlation between radiological and histological changes following root canal treatment. *Journal of British Endodontic Society* **7**, 57–63.

Rubinstein RA, Kim S (1999) Short-term observation of the results of endodontic surgery with the use of a surgical operation microscope and Super-EBA as root-end filling material. *Journal of Endodontics* **25**, 43–8.

Saleh IM, Ruyter IE, Happasalo M, Ørstavik D (2004) Survival of *Enterococcus faecalis* in infected dentinal tubules after root canal filling with different root canal sealers *in vitro*. *International Endodontic Journal* **37**, 193–8.

Salehrabi R, Rotstein I (2004) Endodontic treatment outcomes in a large patient population in the USA: an epidemiological study. *Journal of Endodontics* **30**, 846–50.

Salzgeber RM, Brilliant JD (1977) An in vivo evaluation of the penetration of irrigating solution in root canals. *Journal of Endodontics* **3**, 394–8.

Savarrio L, Mackenzie D, Riggio M, Saunders WP, Bagg J (2005) Detection of bacteraemias during non-surgical root canal treatment. *Journal of Dentistry* **33**, 293–303.

Seltzer S (1988) *Endodontology. Biologic Considerations in Endodontic Procedures*, 2nd edn. Philadelphia: Lea & Febiger, p. 440.

Seltzer S, Turkenkopf S, Vito A, Green D, Bender IB (1964) A histologic evaluation of periapical repair following positive and negative root canal cultures. *Oral Surgery, Oral Medicine, and Oral Pathology* **17**, 507–32.

Senia ES, Marshall FJ, Rosen S (1971) The solvent action of sodium hypochlorite on pulp tissue of extracted teeth. *Oral Surgery, Oral Medicine, and Oral Pathology* **31**, 96–103.

Shuping GB, Ørstavik D, Sigurdsson A, Trope M (2000) Reduction of intracanal bacteria using nickel-titanium rotary instrumentation and various medications. *Journal of Endodontics* **2**, 304–11.

Sidaravicius B, Aleksejuniene J, Eriksen HM (1999) Endodontic treatment and prevalence of apical periodontitis in an adult population of Vilnius, Lithuania. *Endodontics & Dental Traumatology* **15**, 210–5.

Simon JHS (1994) The apex: how critical is it? *General Dentistry* **42**, 330–4.

Simon JHS (1998) Periapical pathology. In: Cohen S, Burns RC, eds. *Pathways of the Pulp*, 7th edn. St Louis, MO: Mosby, pp. 425–62.

Siqueira JF Jr (2001) Aetiology of root canal treatment failure: why well-treated teeth can fail. *International Endodontic Journal* **34**, 1–10.

Siqueira JF Jr, Lopes HP (1999) Mechanisms of antimicrobial activity of calcium hydroxide: a critical review. *International Endodontic Journal* **32**, 361–9.

Siqueira JF Jr, Lopes HP (2001) Bacteria on the apical root surfaces of untreated teeth with periradicular lesions: a scanning electron microscopy study. *International Endodontic Journal* **34**, 216–20.

Siqueira JF Jr, Araújo MCP, Garcia PF, Fraga RC, Dantas CJS (1997) Histological evaluation of the effectiveness of five instrumentation techniques for cleaning the apical third of root canals. *Journal of Endodontics* **23**, 499–502.

Sirén EK, Haapasalo MPP, Waltimo TMT, Ørstavik D (2004) *In vitro* antibacterial effect of calcium hydroxide combined with chlorhexidine or iodine potassium iodide on *Enterococcus faecalis*. *European Journal of Oral Sciences* **112**, 326–31.

Skaug N (2003) Systemic complications of endodontic infections. In: Bergenholtz G, Hørsted-Bindslev P, Reit C, eds. *Textbook of Endodontology*. Oxford: Blackwell, pp. 145–55.

Slavkin H (1999) Does the mouth put the heart at risk? *Journal of American Dental Association* **130**, 109–14.

Snyder DE, Seltzer S, Moodnik R (1966) Effects of N_2 in experimental endodontic therapy. *Oral Surgery, Oral Medicine, and Oral Pathology* **21**, 635–56.

Spångberg LSW, Haapasalo M (2002) Rationale and efficacy of root canal medicaments and root filling materials with emphasis on treatment outcome. *Endodontic Topics* **2**, 35–58.

Stabholz A, Friedman S, Tamse A (1994) Endodontic failures and re-treatment. In: Cohen S, Burns RC, eds. *Pathways of the Pulp*, 6th edn. St Louis, MO: Mosby, pp. 692–3.

Stashenko P (1990) The role of immune cytokines in the pathogenesis of periapical lesions. *Endodontics & Dental Traumatology* **6**, 89–96.

van der Stelt PF (1985) Experimentally produced bone lesions. *Oral Surgery, Oral Medicine, and Oral Pathology* **59**, 306–12.

Strindberg LZ (1956) The dependence of the results of pulp therapy on certain factors: an analytic study based on radiographic and clinical follow-up examination. *Acta Odontologica Scandinavica* **14**(Suppl. 21), 1–175.

Sundquist G, Reuterving C (1980) Isolation of *Actinomyces israelii* from periapical lesion. *Journal of Endodontics* **6**, 602–6.

Svensäter G, Bergenholtz G (2004) Biofilms in endodontic infections. *Endodontic Topics* **9**, 27–36.

Tamse A, Lustig J, Kaplavi J (1999) An evaluation of endodontically treated vertically fractured teeth. *Journal of Endodontics* **25**, 506–8.

Tanomaru Filho M, Leonardo MR, Silva LAB, Utrilla LS (1998) Effect of different root canal sealers on periapical repair of teeth with chronic periradicular periodontitis. *International Endodontic Journal* **31**, 85–9.

Testori T, Badino M, Castagnola M (1993) Vertical root fractures in endodontically treated teeth: a clinical survey of 36 cases. *Journal of Endodontics* **19**, 87–90.

Thoden van Velzen SK, Abraham-Inpijn L, Moorer WR (1984) Plaque and systemic disease: a reappraisal of the focal infection concept (review). *Journal of Clinical Periodontology* **11**, 209–20.

Torabinejad M, Ung B, Kettering JD (1990) In vitro bacterial penetration of coronally unsealed endodontically treated teeth. *Journal of Endodontics* **16**, 566–9.

Tronstad L, Sunde PT (2003) The evolving new understanding of endodontic infections. *Endodontic Topics* **6**, 57–77.

Tronstad L, Barnett F, Riso K, Slots J (1987) Extraradicular endodontic infections. *Endodontics & Dental Traumatology* **3**, 86–90.

Tronstad L, Asbjørnsen K, Døving L, Pedersen I, Eriksen HM (2000) Influence of coronal restorations on the periapical health of endodontically treated teeth. *Endodontics & Dental Traumatology* **16**, 218–21.

Trope M (2003) The vital tooth-its importance in the study and practice of endodontics. *Endodontic Topics* **5**, 1–11.

Trope M, Bergenholtz G (2002) Microbiological basis for endodontic treatment: can a maximal outcome be achieved in one visit? *Endodontic Topics* **1**, 40–53.

Valderhaug J (1974) A histologic study of experimentally induced periapical inflammation in primary teeth in monkeys. *International Journal of Oral Surgery* **3**, 111–23.

Vessey RA (1969) The effect of filing versus reaming on the shape of the repaired root canal. *Oral Surgery, Oral Medicine, and Oral Pathology* **27**, 543–7.

Vire DE (1991) Failure of endodontically treated teeth: classification and evaluation. *Journal of Endodontics* **17**, 338–42.

Von Arx T (2005) Frequency and type of canal isthmuses in first molars detected by endoscopic inspection during periradicular surgery. *International Endodontic Journal* **38**, 160–8.

Walters MJ, Baumgartner JC, Marshall JG (2002) Efficacy of irrigation with rotary instrumentation. *Journal of Endodontics* **28**, 837–9.

Waltimo TMT, Boiesen J, Eriksen HM, Ørstavik D (2001) Clinical performance of 3 endodontic sealers. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **92**, 89–92.

Walton RE (1976) Histologic evaluation of different methods of enlarging the pulp canal space. *Journal of Endodontics* **2**, 304–11.

Walton RE, Torabinejad M (1996) *Principles and Practice of Endodontics*, 2nd edn. Philadelphia: W.B. Saunders Company.

Wang JD, Hume WR (1988) Diffusion of hydrogen ion and hydroxyl ion from various sources through dentine. *International Endodontic Journal* **21**, 17–26.

Weller RN, Niemczyk SP, Kim S (1995) Incidence and position of the canal isthmus. Part 1. Mesiobuccal root of the maxillary first molar. *Journal of Endodontics* **21**, 380–3.

West JD, Roane JB (1998) Cleaning and shaping the root canal system. In: Cohen S, Burns RC, eds. *Pathways of the Pulp*, 7th edn. St Louis, MO: Mosby, pp. 203–57.

Wu M-K, Wesselink PR (1993) Endodontic leakage studies reconsidered: Part I. Methodology, application and relevance. *International Endodontic Journal* **26**, 37–43.

Wu M-K, Wesselink PR (2001) A primary observation on the preparation and obturation in oval canals. *International Endodontic Journal* **34**, 137–41.

Wu M-K, Wesselink PR (2006) Timeliness and effectiveness in the surgical management of persistent post-treatment periapical pathosis. *Endodontic Topics*, in press.

Wu M-K, Roris A, Barkis D, Wesselink PR (2000a) Prevalence and extent of long oval shape of canals in the apical third. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **89**, 739–43.

Wu M-K, Wesselink PR, Walton RE (2000b) Apical terminus location of root canal treatment procedures. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **89**, 99–103.

Wu M-K, van der Sluis LWM, Wesselink PR (2003) The capability of two hand instrumentation techniques to remove the inner layer of dentine in oval canals. *International Endodontic Journal* **36**, 218–24.

Yusuf H (1982) The significance of the presence of foreign material periapically as a cause of failure of root treatment. *Oral Surgery, Oral Medicine, and Oral Pathology* **54**, 566–74.